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Lymphatic Leukemia and Malignant Lymphoma in the Adult

A clinicopathologic study of their interrelationship

By Alf Rausing

LYMPHATIC LEUKEMIA AND MALIGNANT LYMPHOMA
IN THE ADULT

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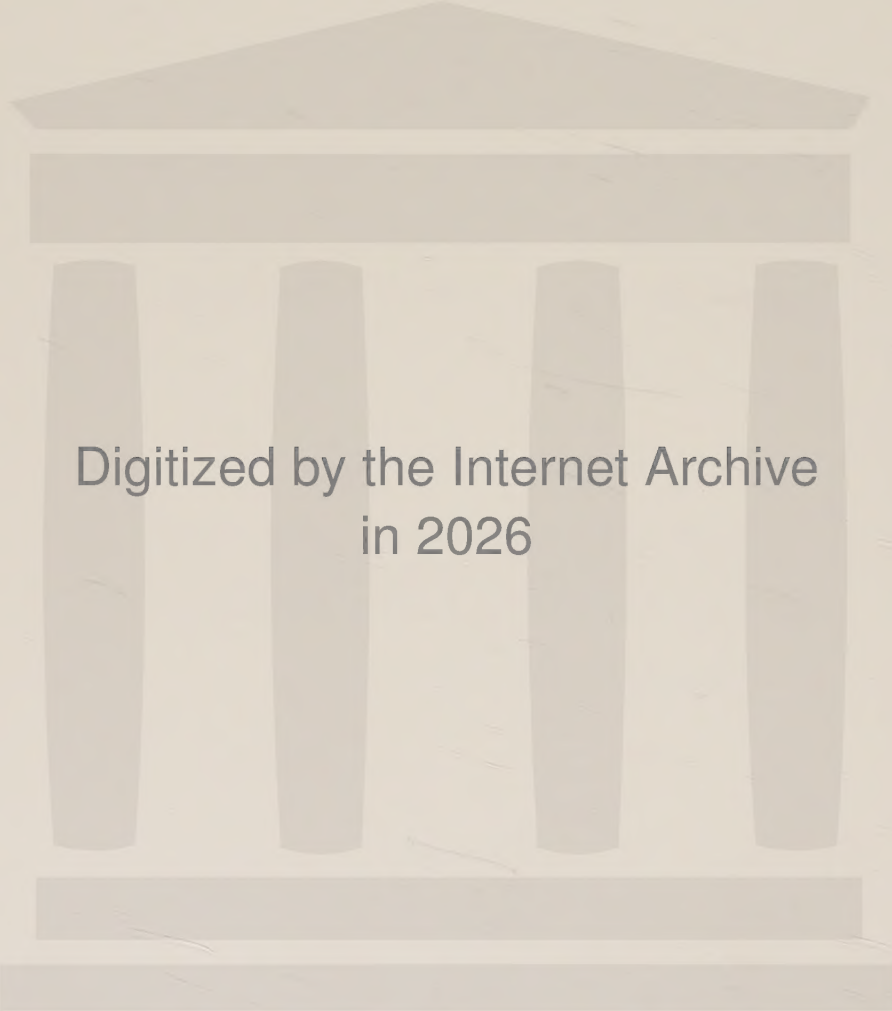
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Translated by L. James Brown



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ABBREVIATIONS

CLL	=	chronic lymphatic leukemia
GER	=	granular endoplasmic reticulum
Hb	=	hemoglobin concentration
HL	=	malignant lymphoma, histiocytic type
IF	=	immature foci of lymph nodes in CLL (described in text, page 23)
IF-n	=	immature foci in necropsy specimens (see text, page 87)
K or L following designation of immunoglobulin class = kappa or lambda		
LLD	=	lymphocytic malignant lymphoma, diffuse
LLN	=	lymphocytic malignant lymphoma, nodular
M/F	=	males/females
M-comp(onent)	=	monoclonal immunoglobulin component
WBC	=	white blood cell count or white blood cells

INTRODUCTION

This work concerns the natural history of, and the relationship between, various forms of lymphatic leukemia and malignant lymphoma, with special reference to the following questions:

1. Does the morphologic picture of the lymph nodes in chronic lymphatic leukemia (CLL) differ from that in aleukemic lymphocytic malignant lymphoma?
2. What are the leukemic manifestations of the various histologic and cytologic forms of lymphocytic malignant lymphoma?
3. How do the histologic, cytologic and clinical pictures in this group of diseases develop from the time of diagnosis to the terminal stage? Special reference is made to the development of histiocytic malignant lymphoma and Hodgkin's disease.
4. Should Waldenström's macroglobulinemia be regarded as a lymphocytic malignant lymphoma and does its development resemble that of other malignant lymphocytic lesions?

Chapter 1

HISTORICAL

The term leukemia was coined by Virchow, who thought that lymphatic leukemia originated in the lymph nodes and assigned this form of leukemia to the group of lymphomas, or lymph node tumours (77). He assumed that the process was neoplastic, but that it was also systemic in that it characteristically involved the entire lymphatic system. But he also described lymphatic tumours in non-lymphatic organs in this form of leukemia as well as localised tumours of lymph nodes, which he called lymphosarcomas and which were not related to leukemia, but ran a progressive and frequently acute course. Virchow thought that the conditions might closely resemble each other and that one could not exclude the possibility of an essential similarity between them (78). According to Virchow, lymphosarcoma gradually becomes generalised, like a metastasising tumour. He also regarded the changes described by Hodgkin in 1832 as lymphosarcomas (24).

In 1865 Cohnheim (10) used the term pseudoleukemia to designate conditions with a leukemia-like picture of the lymph nodes without associated changes in the blood.

In 1871 Billroth introduced the term malignant lymphoma (8).

In 1878 Neuman (51) assumed that all leukemic diseases, including lymphatic leukemia, arose in the bone marrow, an idea which was soon widely accepted.

In 1893 Kundrat (31) distinguished between leukemia and "lymphosarcomatosis" by their distribution and mode of growth, though they were cytologically similar. According to him, leukemia was a primarily generalised systemic disease of the lymphatic system without destructive properties, while lymphosarcomatosis was an invasive tumour that could start in the lymphatic structures of various tissues, including the lymph nodes. Further, he thought that the lesions tended to spread first locally, and later to the lymphatics, and finally also via the blood-stream.

By the turn of the century two forms of leukemia were recognised, *viz.* myeloid and lymphatic. They were divided into acute and chronic forms.

In 1903 Türk (68) claimed that though malignant lymphatic diseases have clinical and anatomic characteristics permitting precise classification of most cases, many transitional forms exist, and one should regard lymphatic leukemia and lymphosarcomatosis as a family of closely related "lymphomatoses".

In 1908 Sternberg (66) introduced the term leukosarcomatosis for designating the combination of leukemia and sarcomatous lymphatic lesions, most often situated in the mediastinum. The leukemia in this condition is, according to Sternberg, characterised by a larger and more immature form of cell than leukemia seen in association with diffuse disease of the lymph nodes. He thought that this condition should be distinguished from lymphomatoses with leukemia. Many cases of acute myeloid

leukemia with tumorous lesions have been described under the name of leukosarcomatosis. Later, Apitz (4) felt that leukemia and sarcomatous lymphatic tumours were fundamentally similar and showed the untenability of the term leukosarcomatosis as used in the literature.

In 1921 Webster (74) shared Türk's view, but used the term lymphadenosis instead of lymphomatosis. He felt that the whole group was not of neoplastic nature.

In Sweden lymphadenosis was for a long time probably the most widely used name for lymph node processes of this type, based on the conception that lymphoma in lymphatic leukemia and in aleukemic lymphocytic lymphoma cannot be distinguished from one another histologically. Tumours arising in tissues other than the lymph nodes and built up of cells recognisable as lymphocytic, have generally been called lymphosarcomas.

The older literature in this field is difficult to analyse because all lymphatic tumours (and often infectious lymphatic hyperplasia) have been included within the term lymphosarcoma. The problem complex was intimately associated with tuberculosis. Moreover, myeloblastic leukemia was often included in series of lymphatic leukemia, and chloroma was often regarded as belonging to malignant lymphoma.

From the beginning of the 20th century it was possible to distinguish Hodgkin's disease from "non-Hodgkin"-lymphomas (57). The 1920s and 1930s witnessed a tendency to a differentiation between tumours of the lymph nodes. The large cell and anaplastic variants of such tumours were often referred to as reticulum cell sarcoma, due particularly to Roulet's work (60). This form of growth was most often not leukemic. From about 1930 clearly lymphocytic tumours were most often referred to in Scandinavia as lymphadenosis or lymphocytic lymphosarcoma, while the term reticulum cell sarcoma was used for a wide variety of lesions of the lymph nodes, whose definitions varied geographically and from time to time. The term aleukemic reticulosis was coined by Letterer in 1924 (38) and has been used to designate various less well defined conditions (see discussion in 35). Brill, Baehr and Rosenthal in 1925 (9) and Symmers in 1927 (67) described lymph node lesions with a follicular (nodular) structure and a relatively benign course. The changes sometimes develop into highly malignant, diffusely growing lesions. Such follicular processes were often called Brill-Symmers' disease, and their neoplastic nature was questioned. They were often not distinguished from follicular lymphatic hyperplasia.

After investigation of a large clinicopathologic material Gall and Mallory in 1942 (18) felt that malignant lymphoma is generally constant in type during its development. They distinguished between lymphocytic and lymphoblastic malignant lymphoma, both of which sometimes had leukemic manifestations. They suggested that the term lymphosarcoma should be omitted because it had been used with varying meaning and because lymphosarcomatosis in the sense of the term used by Kundrat is a component of lymphocytic or lymphoblastic malignant lymphoma. They believed that lymphatic leukemia and malignant lymphoma are different manifestations of one and the same disease.

Rappaport's classification of lymphoma, which closely resembles that of Gall and Mallory, has in recent years been the one most widely used in the English spea-

king countries (55). According to Rappaport, all cytologic types of lymphoma can occur with nodular or diffuse growth. The cytologic types are undifferentiated malignant lymphoma, histiocytic malignant lymphoma and lymphocytic malignant lymphoma, the last-mentioned occurring in a well differentiated and in a poorly differentiated form. The classification also includes mixed histiocytic-lymphocytic malignant lymphoma. The lymphocytic lymphomas can, according to Rappaport, be associated with leukemia with a corresponding type of cell.

In 1937 Isaacs (25) used the term lymphosarcoma cell leukemia for initially aleukemic lymphosarcoma, which later developed into leukemia. He felt that it is possible cytologically to distinguish cells in this form of leukemia from those in "genuine" lymphatic leukemia mainly by characteristics of the nucleolus.

In 1942 Wiseman (79) claimed that one can distinguish chronic lymphatic leukemia from lymphosarcoma cell leukemia, though both conditions may be leukemic or aleukemic. According to him, lymphosarcoma cell leukemia is a manifestation of a neoplastic disease, in contrast with chronic lymphatic leukemia, which he regarded as being of "metabolic" nature.

The term "notched cell leukemia" has been used to designate a lymphatic leukemia with irregular, "atypical" cells, seen in cases of nodular lymphomas (3).

In 1965 Schwartz et al. (63) pointed out the existence of cytologic and clinical differences between CLL and lymphosarcoma cell leukemia. They distinguished two forms of lymphosarcoma cell leukemia *viz.* chronic and acute, and they thought that these should be distinguished from chronic and acute lymphatic leukemia. This distinction was made on the basis of cytologic characteristics of the blood and bone marrow. The picture of the lymph nodes was not described in the various groups. Schwartz et al. gave a practical definition of leukemia contra lymphoma on phenomenologic grounds (involvement of the bone marrow, blood picture, dysfunction of the bone marrow). It is obvious that classification according to these principles may be of practical value, but means that a given case will be recorded as lymphoma or leukemia depending on the hematologic findings at the time of the diagnosis and if the picture of the lymph nodes and the development of the disease are not taken into account, the classification of a given case will be arbitrary.

The term lymphosarcoma cell leukemia has not been widely used. Zacharski and Linman in 1969 (80) shared the view of Schwartz et al. that the condition should be distinguished from CLL because the prognosis is much poorer. It is difficult to grasp whether these authors thought that it was a question of a primarily generalised systemic disease or a secondarily leukemic malignant lymphoma. They disregarded the histologic features of the lymph nodes.

In 1970 Schnitzer et al. (62) studied 18 cases according to the same principles as in the present work. They concluded that lymphosarcoma cell leukemia is the hematologic manifestation of poorly differentiated nodular or diffuse lymphocytic malignant lymphoma.

A type of lymphatic leukemia with some resemblance to CLL but with more immature cells and a poorer prognosis has been called prolymphocytic leukemia by Galton et al. (19). The lymph node pathology of this condition has not been adequately described.

If Rappaport's lymphoma nomenclature is used, the question of terminology is, in my opinion, different, since the word lymphosarcoma is not included and consequently also the term lymphosarcoma cell leukemia should be dropped. Rappaport wrote that well differentiated lymphocytic malignant lymphoma may be the tissue manifestation of CLL and that it is not possible to distinguish an isolated lymphoma of this type from CLL simply on the basis of the histologic picture. This view is shared by several authorities, e.g. Dorfman, who in 1973 (14) wrote that the best differentiated lymphocytic lymphoma is usually a tissue manifestation of CLL.

Lennert has pointed out that the picture of the lymph node in CLL may sometimes be distinguished from aleukemic lymphoma by the fact that the former has clusters of immature cells scattered among the mature ones (36).

In many recent articles, initially leukemic cases are not included in series of malignant lymphomas (e.g. 11,13,54). Dick et al. (13) believed that there is a difference between CLL and well differentiated lymphocytic malignant lymphoma, but that the cytology is exactly the same. However, they excluded leukemic cases from their series of lymphoma.

There is a general agreement that primary aleukemic malignant lymphoma of almost all types can show a notable preterminal release of cells into the blood. Some authors feel that such a release is the consequence of an overwhelming proliferation of the tumour with invasion of blood vessels and that the condition should be distinguished from leukemia in the strict sense of the word, a term which should be reserved for the presence of cells in the circulation, which, so to say, have a natural tendency to occur there.

According to Amromin (1), lymphosarcoma cell leukemia is not leukemia at all. He thinks the condition to be similar to e.g. malignant melanoma with tumour cells in the blood. Elsewhere in Amromin's book it is stated that it may be impossible to distinguish histologically between the picture of the lymph nodes in CLL and in lymphosarcoma (2). It is difficult to understand this line of thought. Leukemic conditions with identical morphology should, according to him, thus sometimes be leukemia, and sometimes not.

A point which, in my opinion, contributes to the nosographic confusion in this field is that aleukemic malignant lymphomas are often investigated only with the aid of biopsy of the lymph nodes; leukemic conditions, with cytology of the bone marrow. Leukemic diseases are treated by hematologists; aleukemic lymph node diseases by radio-therapists. The classification of a given case will therefore depend to no little extent on the methods used by the physician who makes the diagnosis and treats the patient according to his professional background and general attitude.

PRESENT INVESTIGATION. This investigation concerns a series of biopsy specimens of lymph nodes showing lymphocytic malignant lymphoma with respect to the blood and bone marrow status of the patients at the time of diagnosis and during the further course of the disease. The patients were followed until death and were subjected to complete necropsy. The picture of the lymph nodes in clinical characteristic CLL is defined and the leukemic manifestations of other lymphocytic malignant lymphomas are described.

THE CONSTANCY OF THE TYPE OF CELL AND THE MODE OF GROWTH IN THE INDIVIDUAL GROUPS OF MALIGNANT LYMPHOMAS vary according to the literature. Gall and Mallory (18) claimed that the picture is most often the same during the course of the disease and in various parts of the pathologic infiltrates, but they admitted that exceptions occur and that transitional forms are seen between the different groups and that such cases are seen where the process changes in morphologic character during its development. Custer and Bernhard in 1948 (12) found a high frequency of such transformations. They reported a change in type in 30 - 40 % of all lymphatic tumours, including Hodgkin's disease. Rappaport also felt that such changes were common in some groups and stated that the type of cell has a tendency to dedifferentiate during the course of the disease and that a nodular mode of growth has a tendency to become diffuse and that the mixed lymphoma group tends to become monocellular in type, most often by developing into malignant lymphoma of histiocytic type. Kim and Dorfmann (30) found a variation of the picture in different parts of the infiltrate in 16 % of untreated cases of non-Hodgkin's lymphoma examined with extensive biopsy at laparotomy. They felt, however, that the constancy of the type must be regarded as high in this group of diseases. But such histologic and cytologic changes are obviously not rare in aleukemic malignant lymphomas. In typical CLL such changes have been touched upon only in case reports or small series and many authors claim that they are so rare that they represent coincidence of two diseases. The transformation of chronic myeloid leukemia to myeloblastic leukemia is well known and occurs in more than every other patient with chronic myeloid leukemia and must therefore be regarded as a natural development of this disease. Terminal blastic transformation in CLL is flatly denied by some authors. Mørk Hansen reported terminal blastosis in 3 of his series of 189 cases of CLL (50).

As will be apparent from a later section in this book, a change in cell morphology in a more "immature" direction is common in CLL. The "new" type of proliferation, however, has not the tendency of the myeloblasts to pass over into the circulation, and therefore the changes are rarely diagnosed intra vitam. Instead of blastic leukemia the new type of proliferation tends to be some other type of malignant lymphoma.

Judging from the literature, Richter was the first who described a case of CLL and reticulum cell sarcoma in 1928 (58). Earlier observations of the development of large sarcomatous lesions in CLL may, of course, have represented the same phenomenon, but since the term reticulum cell sarcoma and the like had not been used before, such cases were probably described as CLL with lymphosarcoma, leukosarcoma etc. The single cases or small series reported later show that the new type of proliferation is either Hodgkin's disease or reticulum cell sarcoma, most often Hodgkin's disease. A coincidence of Hodgkin's disease and lymphatic leukemia was described as early as 1906 by Warthin (72). Lortholary et al. reported 4 cases in 1964 and suggested that both combinations (CLL-Hodgkin's disease and CLL-reticulum cell sarcoma) should be called Richter's syndrome (41). They gave a survey of earlier literature and stated that about 25 cases had been published. Their survey was, however, not complete and, including later publications, I know that some 50 papers have been published on

this question. All the published cases are not clearly representative of one or both of the claimed conditions, for which reason it is meaningless to review the literature in detail. Recent surveys of the literature are to be found in Vaurabourg (73), and in Long and Aisenberg (40).

To explain the coincidence of two morphologically different processes in the same tissue, earlier authors have used essentially one or the other of the following theories:

1. A coincidence of two unrelated diseases. Wildhack was inclined to accept this hypothesis as he said that the coincidence (CLL-Hodgkin's disease) is extremely rare (76). Similar views have been presented by Lokich and Moloney (39) and by Givler (21) and several others.
2. A lymphatic leukemoid reaction in a patient with Hodgkin's disease or a sarcomatous tumour. The time of onset of the two conditions usually argues against this theory because leukemia has generally been diagnosed long before the supposed onset of "reticulosis". But Marchal et al. felt that such an explanation might be reasonable in their case (45).
3. The diseases differ in nature but have the same etiology. Such opinions have often been published (e.g. 29,41).
4. There is a histogenetic relationship between the diseases explaining the transition of one picture to another. This theory is probably the one most widely accepted (e.g. 12).
5. Treatment of the condition which appeared first has induced the second. This point has not been discussed in detail because only few cases have been reported and they have been treated in different ways.

The only opinion shared by all authors is that these changes are rare. In the present material this was not the case. It was therefore considered legitimate to study these transformations anatomically and clinically. If CLL is a lymphocytic lymphoma similar to the aleukemic lymphocytic lymphomas, one might a priori imagine a similar development in this respect, which was also found to be the case.

PRESENT INVESTIGATION. This paper reports a series with detailed histologic post mortem examination at which sarcomatous changes of the type described above are often revealed in CLL. As far as I know, no such investigation has been published before, presumably because only few tissue blocks are generally examined and focal changes are therefore readily missed.

WALDENSTRÖM'S MACROGLOBULINEMIA (see 69,70,71) is difficult to classify. The clinical picture is often dominated by symptoms due to the macroglobulin in the circulation and by unspecific symptoms, such as fatigue and loss of body weight. Surveys of various aspects of the disease have been published by McCallister et al. (47), Martin (46) and by Mac Kenzie and Fudenberg (43), and others. Enlargement of lymph nodes or the spleen suggesting lymphoproliferative disease is by no means a regular finding. But infiltration of the bone marrow by lymphatic cells is the rule, and it is widely accepted that the anatomic basis of the disease is infiltration by lymphatic cells, the extent and site of the infiltration varying as well as the cytological picture from one case to another. Surveys of the morphologic changes in macroglobulinemia have been published by Zollinger (81), Dutcher and Fahey (16),

Le Beaux and Ganter (33), Harrison (23), Rywlin et al. (61) and others. The changes in the bone marrow are the most constant findings and consist of infiltration, often diffuse, sometimes focal, of lymphocytes, plasma cells and transitional forms (59). Mast cells are often abundant. Histiocytes are usually increased in number and often contain abundant iron pigment. These forms of cells are usually those which constitute the extramedullary infiltrates, if any. The picture of the lymph nodes in characteristic cases resembles that seen in lymphocytic malignant lymphoma, but the infiltration is less dense and the changes are not obligatory. Several variants of this "classical" cytological picture are found. Sometimes the picture of the bone marrow is entirely plasmocellular and resembles that seen in myeloma. Sometimes the picture cannot be distinguished from that of CLL, and even clinically the condition may resemble CLL (26). Dutcher and Fahey (16) described PAS-positive inclusions in nuclei or cytoplasm, but such inclusions are not obligatory and can be seen also in other diseases and in reactive conditions (see e.g. 23). Many authors' series contain cases, which, according to their descriptions, should be regarded as "reticulum cell sarcoma" (82 with survey of the literature) or Hodgkin's disease (43) or sometimes lymphatic lesions of the type "lymphosarcoma" (43, and others), which may be osteolytic (e.g. 75). These cases may also be clinically more "malignant" than others and thus behave like the morphologic entity in question and some authors regard the macroglobulinemia in such cases as "secondary" to malignant lymphoma and as some disease other than classical Waldenström's macroglobulinemia. The problem is thus briefly whether it is a question of macroglobulinemia with malignant lymphoma or malignant lymphoma with macroglobulinemia. The untenability of a primary and a secondary form in this sense has been pointed out by Mac Kenzie and Fudenberg, who reported cases which began as a "primary" form and afterwards became more malignant (43). They felt that it might be a question of a proliferation of immunoglobulin-producing cells, that can vary from an entirely benign disease to rapidly progressive lymphoma. Similar views were presented by Rywlin et al. (61). The problem is complicated further by the fact that many malignant lymphomas and lymphatic leukemias can have an M-component of macroglobulin nature without clinical evidence of Waldenström's macroglobulinemia (see e.g. 49) and, as has been shown by e.g. Stein et al. (65), tumour tissue from various lymphomas can sometimes contain abundant immunoglobulins, usually of type IgM. These authors therefore deny the existence of macroglobulinemia as a pathologic entity and regard the condition rather as IgM-secreting lymphoma of varying types. Such an assumption is, however, partly refuted by the findings by Mac Kenzie and Fudenberg, who studied tumours, histologically resembling "lymphosarcoma and Hodgkin's disease", from patients with macroglobulinemia (43). Using the immunofluorescence technique they found no production of IgM in tumour tissue, but they did find it in plasma cell-like elements in the bone marrow. Similar findings have been reported by Palutke and Mc Donald (52) in cases of poorly differentiated lymphocytic lymphoma with macroglobulinemia.

PRESENT INVESTIGATION. In my opinion, macroglobulinemia is a low-grade malignant lymphoproliferative disease, closely related to other low-grade lymphatic

malignant diseases such as CLL. Like this condition, macroglobulinemia has a tendency to progress and to develop a more malignant histologic and clinical picture. The morphologic appearance and the degree of clinical aggressiveness of a given case thus depend on the stage in which the disease is first seen. It is possible that the cells, when developing in this manner, assume tumour-forming properties and lose the capacity of macroglobulin production.

To test this hypothesis and to define the morphologic picture in cases diagnosed clinically as macroglobulinemia I examined all cases of the disease investigated post mortem in the same way as cases of CLL and aleukemic lymphocytic lymphoma. Though the material was small, it was felt that it deserved publication because only few series of macroglobulinemia with extensive routine post mortem examination are on record.

Chapter 2

INTRODUCTORY REMARKS ON LYMPHOMA NOMENCLATURE

The classification of malignant lymphoma has, as pointed out in a previous section, been the subject of intense debate. No classification system has hitherto been universally accepted for any length of time and it is obviously difficult to find descriptive definitions to standardise the criteria for a diagnosis.

For a long time the most widely used nomenclature was based on the terms lymphosarcoma and reticulum cell sarcoma. These names have been used with such different meanings that they are now confusing. In recent years Rappaport's nomenclature has been used most in English-speaking countries (55). It is clinically valuable and terminologically simple. It is based on the histologic arrangement of the cells, diffuse or nodular, and on the degree of differentiation of the cells and their assumed cytogenesis. In the present investigation lymph node tumours with initially clearly lymphocytic character and their relation to lymphatic leukemia were studied. The picture of the lymph nodes in CLL is believed by Rappaport to reflect one type of malignant lymphoma. One of the questions posed in the present investigation was whether the picture of the lymph nodes in CLL differs from that of non-leukemic lymphoma. Since this was found to be the case, it was not possible to group the appearances of the lymph nodes according to a classification of lymphomas, where CLL is grouped together with some other form of lymphoma. It is generally accepted that, histologically, lymphoma can be divided into two groups, *viz.* of diffuse and nodular growth. This principle was therefore applied: lymphocytic malignant lymphoma, diffuse, (LLD) and nodular (LLN). Rappaport's classification is based not only on these two types of growth of the lymphocytic lymphomas, but also on the differentiation of the cells. Rappaport himself admits that the differentiation may sometimes be difficult to determine. It is hazardous to apply the term differentiation to lymphatic cells because the circulating lymphocytic population, morphologically well differentiated cells, are not final functional stages and can develop into cells of less well differentiated appearance. Morphologically less well differentiated cells may therefore be cells which have not reached, or which have passed, a well differentiated stage. It is not yet known whether "poorly differentiated" lymphoma cells should be regarded as representing the one or the other stage of the life-cycle of the lymphocytes. These cells are abnormal and it is not known whether their life-cycle is the same as that of normal cells. To describe lymphoid cells in this connection I decided to replace the term differentiation by the terms maturity and atypia. They are perhaps unsatisfactory, but they describe 2 different aspects which are not necessarily parallel and which cannot be distinguished by the term differentiated. The same objection may be raised against maturity as against differentiation, namely that an immature cell may be younger or older than a mature one. The word is used descriptively in such a way as will be defined later and was chosen only as an acceptably brief term for describing the variables of cell morphology in question.

The term atypia is not really satisfactory in this connection either. It may be questioned whether we know the exact morphologic appearances of all stages of the life-cycle of the lymphocytes. The problem is particularly complex because the lymphatic tissue is widespread in the body and because lymphatic cells may differ in appearance from one part of the body to another. Lymph nodes and other peripheral lymphoid organs contain several functional compartments which may differ morphologically. It is therefore difficult to define an atypical lymphoid cell. A practical definition in the sense used in this publication is given later, but it is only a "working term".

That the term differentiation as used by Rappaport is of prognostic significance in lymphocytic lymphoma appears obvious from the literature (27, and others). It may, of course, be used purely descriptively like mature-immature, but I have found that the special aspect of the problem of lymphoma studied in this investigation, namely leukemic manifestations of lymphocytic lymphoma, is easier to study with the aid of 2 variables which are here called degree of atypia and degree of maturity.

There are other obvious weaknesses of Rappaport's classification, such as the word histiocytic for the tumour group most closely corresponding to the older group of reticulum cell sarcoma. There is no evidence that the cells in these tumours have anything to do with such normal cells as are called histiocytes or reticulum cells. Tumours falling morphologically within the definitions of this group of Rappaport's may differ microscopically (and clinically) and the group may comprise several biologic entities. The group of mixed histiocytic-lymphocytic lymphoma appears to suggest a mixture of 2 types of cells, which a priori appears less likely for a relatively common form of tumour.

New classification systems have been formulated in an endeavour to avoid these weaknesses of Rappaport's system (Lukes and Collins, 42, Kiel-classification, 20, Beard, 5, Dorfman, 15, Bennet et al., 6). I feel convinced that some of these systems have theoretical advantages. They are based on theories assuming that lymphoma cells have a counterpart in a certain stage of the lymphocytic life-cycle, and to some extent, on immunological characteristics. No large clinicopathologic studies have been presented where they have been applied and compared, and until such studies are available it does not appear justified to recommend one or the other. From combined biopsy and necropsy experience with malignant lymphomas and lymphatic leukemia I am convinced that it is common for these diseases to change their morphological picture during their course and that many of the pictures described in the above nomenclatures are, or may sometimes be, different developmental stages of the same basic disease. A full understanding of their nature requires a survey of morphologic and clinical characteristics from the first symptom or sign until death. To study this aspect of disease is enormously difficult as it requires a large material of cases carefully examined on many occasions, and subjected to complete necropsy. The present material is far from ideal, primarily because of its small size, but, to my knowledge, no ideal material exists anywhere. This series is presented for what it is worth, with full acknowledgement of its defects. I have chosen a nomenclature which is as simple, conventional and non-committal as possible, in order to be understood by the reader, whether clinician or pathologist. The terms are, in a general way,

easy to translate into those of the above-mentioned systems, however, and the reader who is conversant with them is recommended to consult chapter 12 after chapter 4.

Rappaport's nomenclature will be used in the present investigation, but without the term differentiation. Most readers probably are familiar with the definitions of lymphocytic and histiocytic types of malignant lymphoma and those desiring further details are referred to Rappaport (55). Tumours primarily classified as malignant lymphoma of undifferentiated or histiocytic type are not included in the study, but since many lymphocytic tumours finally become histiocytic that term must be used. In this situation these tumours are always diffuse and will therefore be referred to as "HL", thus meaning malignant lymphoma of histiocytic type with a diffuse mode of growth.

The terms used are therefore:

Lymphocytic malignant lymphoma, diffuse (LLD)

Lymphocytic malignant lymphoma, nodular (LLN)

Histiocytic malignant lymphoma, (HL).

The lymphocytic lymphomas are subgrouped in a way described in chapter 4.

Chapter 3

MATERIAL AND METHODS

The material consisted of adults who had died in Malmö during a 17 year period (1957 - 1973). Malmö is a town situated in the south of Sweden and has about 250,000 inhabitants. The town has only one general hospital, one infirmary for geriatric and chronic diseases and one mental hospital. All three hospitals are served by one institute of pathology. The necropsy frequency is high. More than 95 % of all persons dying in the hospitals in the town are examined post mortem. This means about 70 % of all persons dying in the town. The corresponding figure for 1957 was about 50 %. The social structure of the population is such that practically all persons who die from serious chronic diseases do so in hospital; the frequencies given therefore hold approximately also for the total population of the town.

All NECROPSIES were performed in a standardised way during the study period. Gross examination included intracranial structures, the throat including the larynx and tonsils, the mammae, intrathoracic and intraabdominal organs, retroperitoneum and the pelvis as well as the testes, vessels and soft parts of the femora and the vertebral column. The lungs (at least one section from each lobe) and kidneys (at least one section from each kidney), liver, spleen and heart (at least one section from each organ) were regularly examined microscopically. Also sections of the vertebral bone marrow, and of the prostate were usually examined. When indicated, gross lesions were examined microscopically. Tumours and suspected neoplastic lesions of the internal organs were always examined histologically. In cases with previously known or suspected lymphoma or leukemia also the bone marrow from the femur and lymph nodes were examined microscopically. Investigation of the lymph nodes usually comprised the supraclavicular, mediastinal, axillary, paraaortic and inguinal nodes.

Biopsy and necropsy specimens were fixed in neutral formalin and treated according to routine histotechnical methods. The sections were stained routinely with hematoxylin and eosin. The biopsy specimens from the lymph nodes were also stained according to Giemsa and with per-iodic acid Schiff (PAS) and with silver impregnation for reticulin.

ASPIRATION BIOPSY SPECIMENS OF THE BONE MARROW had been obtained at the department where the patient had been cared for. The material usually consisted of a sternal marrow aspirate. In most cases only cytological smears had been obtained. They had been stained routinely with May-Grünwald-Giemsa. In most cases blood smears had also been obtained at the same time as the bone marrow specimens and were still available. The quality of the smears varied widely and many of them were diluted with blood and showed artefacts. Since histological sections were available in only a small number of cases, it could not be decided to what extent the smears were representative of the bone marrow, and systematic differential counts were regarded as misleading. In those cases where percentages are given in the text,

the smears were judged as representative. The figures give the percentage of all nucleated bone marrow cells. 500 cells were counted.

THE NECROPSY PROTOCOLS were studied to facilitate evaluation of the gross findings.

CLINICAL RECORDS were available for all cases. They varied widely regarding the details. Most cases diagnosed as CLL had been subjected to an extensive hematologic investigation at the department of internal medicine as had cases classified as malignant lymphoma and treated at the department of radiotherapy.

The institute of pathology has a card index system comprising all biopsy specimens from 1957 on. This index was examined for all patients.

THE PATHO-ANATOMIC NOMENCLATURE varied during the period covered by the investigation, but, when possible, in the analysis of the cases Rappaport's lymphoma nomenclature was used with the modification described above.

Infiltration outside lymph nodes is described as tumorous if grossly visible, destructive lesions were found.

The cases are referred to by their necropsy number. A list with a diagnosis of the cases referred to is given in the end of the book.

THE MICROSCOPIC ILLUSTRATIONS are arranged to follow the text as closely as possible. Exceptions are made, however, to facilitate comparison. The photomicrographs are referred to as (fig. with an Arabic numeral) and figures in the text as (fig. with a Roman numeral).

DEFINITIONS. The normal range of the number of white blood cells in the peripheral blood was set at 4,000 to 10,000/ μ l, which is the normal range used at the hospital laboratory. For the same reason the normal range of percentage of lymphocytes in the peripheral blood was taken as 20 - 45 %. The term leukemia as used here is defined as follows: white blood cells more than 10,000 / μ l with more than 45 % lymphocytes. Here lymphocytes are to be understood as any type of lymphocytic cell, also atypical and immature. Objections may, of course, be raised against this definition and cases with other diseases can show higher percentages of such cells, but in view of the composition of the material, i.e. firmly diagnosed lymphoproliferative diseases, it was considered acceptable.

LYMPHOCYTES. A mature lymphocyte is to be understood as one whose nucleus is of coarse chromatin structure and/or exhibits no visible nucleolus in smears stained with May-Grünwald-Giemsa. An immature lymphocyte is to be understood as a cell with lymphocytic characteristics, but with clearly visible nucleolus and a less pachychromatic nucleus than that of the normal small lymphocyte. The term prolymphocyte is contained within this group. The cell in question is described later. Cells with these characteristics were thus not called atypical unless they had the following characteristics.

The term atypical lymphocyte designates a cell with structural characteristics assigning it to the lymphocytic series, but with traits which do not occur in lymphocytes in normal persons in the sites and situations in question. Atypical features were generally irregularities in nuclear shape or structure and/or obvious discrepancy in the nuclear/cytoplasmic relation in respect of size or maturity.

The words mature and immature in the above definitions are used in their conventional morphologic sense and say nothing about my opinion of the physiological characteristics of the cell.

Blast cells are to be understood as cells without distinctly lymphocytic features and with distinct nucleoli and finely dispersed chromatin.

Some other types of cells, not conforming with these definitions, are described in the text.

The number of cells with immature features (immature lymphocytes + blast cells) were graded + to +++ in smears. It is obvious that it is difficult to judge the structure of the chromatin exactly and sometimes the visibility of the nucleolus in the individual cell if the smear is of poor quality. The cases were grouped according to the general impression of the smear without any attempt at differential count: +, only single cells with immature features (a study of some technically satisfactory smears showed that the percentage in this group was less than 5). +++, the majority of the cells had immature features (over 50 %). ++, other cases. This classification is, of course, subjective, but the margin between the groups is wide and the results are readily reproducible. The cell characteristics extracted from the clinical records are given in inverted commas. "Lymphoblasts" thus indicates that the laboratory assistant had judged the cells as such and the classification is not based on cytochemical studies or the like.

DATA ON SURVIVAL are calculated from the time of the clinical diagnosis or from the time when biopsy had retrospectively shown a clear picture of lymphoma. These figures are naturally of only limited value because the disease had existed for a varying time before the diagnosis.

Unless some other disease was detected at necropsy, the lymphoma was regarded as the cause of death. When co-existing serious diseases were detected, the probable cause of death was decided from clinical data and the findings at necropsy.

THE TREATMENT given varied in type and duration from one department to another and a detailed description of the choice of therapy and the results achieved would require too much space in this presentation. No distinction was made between the different types of radiotherapy. From 1963 cobalt radiation was used.

THE IMMUNOGLOBULIN LEVELS were extracted from the reports of electrophoresis. The methods for determining the immunoglobulins and the normal values varied during the period in question and when exact values are given in selected cases, it is only to emphasise the development in a case or the like. The terms high value and low value are to be understood as relative to the normal value used at the central laboratory at the time in question. Typing of immunoglobulin components has sometimes been made in material saved from an earlier occasion (I thank Dr. Anders Grubb, Chemical Central Laboratory, Malmö General Hospital, for help with such determinations). Sometimes no material was available for typing and in such cases the components are referred to by the terms used in the original reports.

In many cases the immunoglobulin level was investigated on several occasions during the course. "Early" is to be understood as during the first half of the course, roughly, and "late" as the latter half of the course. If the patient survived less than

one year after the diagnosis was made, all examinations are regarded as "late".

THE MATERIAL WAS SELECTED IN THE FOLLOWING WAY.

1. All necropsy cases of histologically or clinically diagnosed lymphatic leukemia, lymphocytic malignant lymphoma or macroglobulinemia, or cases with some variant of these diagnoses were reviewed and accepted if the disease initially was preponderantly of lymphocytic type. Cases with isolated soft tissue tumours without involvement of the lymph nodes, spleen, tonsils or bone marrow were not included.
2. All cases diagnosed as non-Hodgkin's lymphoma or lymphatic leukemia on the basis of biopsy specimens and of preponderantly lymphocytic type were examined in respect of the further development and are included irrespective of the diagnosis at necropsy provided this had been done within the period of study. Aleukemic cases were thus included only if the lymphoma had initially been preponderantly of lymphocytic type, but independently of maturity and atypia. All cases of lymphatic leukemia were accepted irrespective of the histologic picture of the lymphoma in biopsy specimens, if any, and independently of the appearance of the necropsy specimens.
On the basis of blood and bone marrow smears some cases, originally classified as CLL, were excluded after reclassification as Sézary's disease or leukemic reticulo-endotheliosis (hairy cell leukemia). No cases of these conditions are included in the material.
3. Cases with a clinical diagnosis of macroglobulinemia were judged. In most of them some intravital or post mortem morphologic examination had produced evidence of lymphoproliferative disease and the case was then accepted. A few cases were excluded because no material revealing morphologic evidence of lymphoproliferative disease was available.

In most of the cases in the series the diagnosis of malignant lymphoma or lymphatic leukemia was verified at necropsy. In a few cases post mortem did not reveal any diagnostic changes, but the cases are nevertheless included because of a firm clinical diagnosis. The clinical criteria for the diagnosis of CLL are difficult to determine because the patients emanated from different departments and a long period was covered, but in such cases where the necropsy specimens did not show diagnostic changes the case was accepted only if intravital examination of the bone marrow or lymph nodes had produced a firm diagnosis.

Cases where the onset was characterised by purely blastic leukemia are not included.

Two patients living outside Malmö, but examined post mortem at the hospital, will be discussed because they elucidate interesting aspects of the problem under discussion. They are not included in the tables or in the frequencies, which thus represent the situation in a defined population.

DESCRIPTION OF THE MATERIAL. The material consisted of 160 cases examined post mortem. In 80 cases smears were available from at least 1 intravital examination of the bone marrow (up to 8 examinations in some patients). At least 1 biopsy specimen of a lymph node of acceptable technical quality was available in 41

cases and in many cases also a lymph node aspirate as well as a spleen aspirate or some other histologic or cytologic biopsy material of interest in the diagnosis of the basic disease.

The age limit for the search was set to 20 years, but the youngest patient was 33 years old. All the patients were Swedish citizens of Caucasian race. The age and sex distribution of the entire necropsy series at the institute during the period in question is given in fig. I. In 114 cases the diagnosis was CLL or lymphatic leukemia. Seven cases had a diagnosis of macroglobulinemia Waldenström.

Of the 2 cases from outside Malmö the diagnosis was macroglobulinemia Waldenström in one and macroglobulinemia Waldenström + CLL in the other.

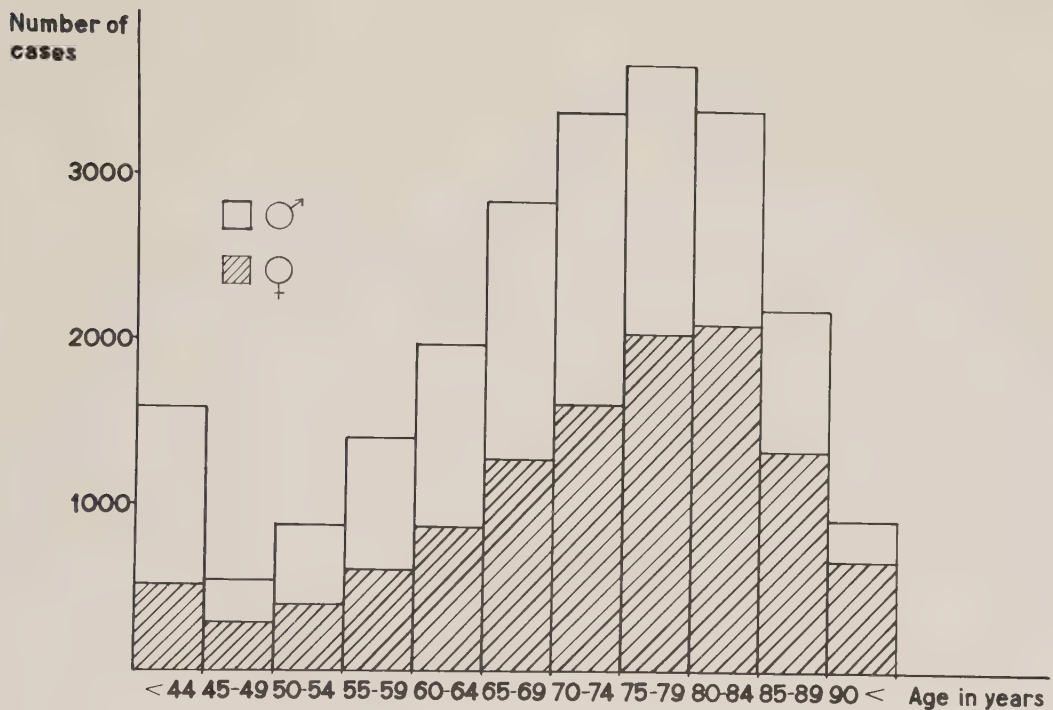


Fig. I. Age and sex distribution of total necropsy series 1957 - 1973.

DISPOSITION OF THE MATERIAL:

CHAPTER 4: Study of the lymph node biopsy specimens.

Classification according to histological picture. Clinical characteristics of these groups. Picture of bone marrow and peripheral blood. Necropsy findings. Discussion of the relation between malignant lymphoma and lymphatic leukemia.

CHAPTER 5: Study of the bone marrow aspirates.

Classification according to cytologic picture of the bone marrow. Clinical characteristics of the group classified as CLL. Necropsy findings. Clinical and morphological

findings in the group with many immature cells. The group of non-leukemic lymphocytic lymphoma of the bone marrow. Some illustrative case reports. Cases classified as macroglobulinemia. Cases difficult to classify. Discussion of the bone marrow cytologic picture and its relation to the histologic appearance of the lymph nodes.

CHAPTER 6: Necropsy series.

Classification of cases not examined with lymph node biopsy or bone marrow aspiration. Technical difficulties with necropsy specimens. Some data on the necropsy material as a whole after grouping.

CHAPTER 7: Macroglobulinemia series.

Morphologic characteristics of lymph nodes, bone marrow and other organs of cases clinically diagnosed as macroglobulinemia. Sarcomatous transformation in this group. Discussion of the possibilities of characterising this diagnosis morphologically.

CHAPTER 8: Studies of the immature cells in CLL.

The correlation between immature cells in lymph nodes, bone marrow and peripheral blood. The relation between the immature cells of CLL and so-called prolymphocytic leukemia. The immature cells in necropsy specimens. Correlation between immature cells and monoclonal immunoglobulin components.

CHAPTER 9: Studies on sarcomatous changes in CLL and other lymphocytic lymphomas.

Frequency of development of histiocytic malignant lymphoma (HL) and Hodgkin's disease in CLL. Clinical characteristics of these cases. Topography and pathology of the lesions. Development of HL in other lymphoma groups. The relation between HL and monoclonal immunoglobulin components.

CHAPTER 10: Special histologic and electron microscopic investigations of immature foci of lymph nodes in CLL, and of HL in CLL.

CHAPTER 11: General discussion with special reference to the relation between CLL and HL.

CHAPTER 12: Concluding remarks on the present situation regarding the nomenclature of malignant lymphoma and lymphatic leukemia.

Chapter 4

THE BIOPSY SPECIMENS OF THE LYMPH NODES

I. Classification according to histological picture.

The degree of differentiation in the sense of the word used by Rappaport is sometimes difficult to determine. Few lymphomas have a really homogenous picture. As pointed out by Rappaport, even the best differentiated tumours contain a certain amount of immature or atypical cells. In doubtful cases classification is decided by the relative amounts of the different cells. In this work it appeared important to separate atypical and immature as described earlier. In the present material two main groups could be distinguished:

A. Tumours with a component of cells, which in histologic sections could not be readily separated from lymphocytic cells in the normal diffuse lymphatic tissue (i.e. non-atypical cells).

B. Tumours without lymphocytes of such normal appearance.

In category A a consistent feature was the presence of a special type of immature cell, which was round or slightly indented and had a nuclear diameter some 50 % larger than a normal small lymphocyte. The cell in question had one large, generally centrally situated nucleolus. It had some slight marginal chromatin condensation and moderate amounts of cytoplasm, staining moderately basophilically, or grey-blue with Giemsa. Three types of tumours could be separated within this category.

1. The first group was dominated by small, apparently normal or almost normal lymphocytes (fig. 3) and evidently contained all clinically characteristic cases of CLL. The above-mentioned immature cells were always demonstrable. The group was further defined by foci, which in low magnification appeared as light areas (fig. 1). The foci varied widely in number and size but were often diffusely and evenly distributed throughout the node. They generally contained a small vessel. They had no constant relation to the high endothelium, postcapillary venules, which were always present in this process. The foci were not sharply outlined against the surrounding tissue (fig. 2). They contained the aforementioned immature cell in greater abundance than the surrounding tissue, but the size of the majority of cells was intermediate that of such immature cells and small lymphocytes (figs. 2, 4, 148). These intermediate cells had discernible nucleoli, though not so large as those of the immature cells described above, and a chromatin condensation and amount of cytoplasm intermediate between that of mature lymphocytes and of the large immature cells. The intermediate sized cells will hereinafter be called prolymphocytes (figs. 4-7). Their functional characteristics are not clear, however. In contrast with what is generally stated about CLL in the literature mitotic figures were very numerous in the above described foci and always appeared to be dividing prolymphocytes or large immature cells. The foci will henceforward be called immature foci (IF). This histologic type will be called lymphocytic malignant lymphoma, diffuse, 1 (LLD-1). The IF are described in

further detail and discussed in chapters 8, 10 and 11.

2. A small group of tumours, consisting only of two cases, was clearly recognized, where the dominating cell was the prolymphocyte described above. The large immature cells were numerous. Only few mature lymphocytes were present. As prolymphocytes were diffusely distributed no IF were apparent. Mitotic figures were very numerous. This picture was called lymphocytic malignant lymphoma, diffuse, 2 (LLD-2) (figs. 10, 11). According to Rappaport's definitions, the picture should be called poorly differentiated, but it was evident that the picture closely resembled the IF of the nodes in LLD-1, as described above.

3. Tumours with a more polymorphous appearance. The large immature cells were present, but they were often somewhat atypical, and apparently normal lymphocytes and prolymphocytes, but no IF. Further, a certain amount of atypical lymphocytes similar to those described below were present. In many cases the atypical cells outnumbered the non-atypical ones. The picture was called lymphocytic malignant lymphoma, diffuse, 3 (LLD-3) (figs. 20, 30, 37, 172).

Category B had only occasional or no non-atypical cells. The atypia consisted of irregularity in the shape of the nuclei, usually in the form of one or more deep clefts or general irregularity of the nuclear shape. However, the chromatin structure was generally coarse, and gave the cells a lymphocytic appearance. A small nucleolus was often seen. Mitotic figures were numerous. In some tumours the cell size was similar to that of the mature lymphocytes of LLD-1, in others the cells were considerably larger. The range of variation in size was always wider than that of the mature cells of LLD-1. This kind of tumour was called lymphocytic malignant lymphoma, diffuse, 4 (LLD-4) (figs. 40, 41, 50-52). There was no sharp border between the small-cell and the large-cell types. No IF were seen and only occasional or no prolymphocytes, but a varying number of more immature and blast-like cells were present. They were smaller than the large immature cells of the first category and did not have their regular shape and huge nucleolus (figs. 50-52). Often several smaller nucleoli were present, generally situated close to the nuclear membrane. These cells were similar to such as are found in the nodules of the nodular lymphomas and corresponded to the "histiocytes" of Rappaport. Thus, the tumours in question were to some extent of Rappaport's type mixed histiocytic-lymphocytic lymphoma. When the lymphocytic cells markedly predominate, the case should, according to Rappaport, be called lymphocytic, as was done here. It is, however, evident that the classification as lymphocytic or mixed is to a certain degree arbitrary. In all tumours in this group blast-like cells constituted at most about 10 % of the total number of cells and tumours with more immature cells of this type were not included in the study. In some cases the blast-like cells had to be searched for under high magnification for a considerable time before they could be found. However, no tumour was found where blast-like cells were completely absent. Owing to the general irregularity of the cells and the variation in size and maturity of the non-blastic component, the two types of cells were not always readily recognized, but a close study always revealed both types. No IF were ever seen in this group, but often an insignificant "cloudiness", faintly resembling nodularity (fig. 49). The borderline between well differentiated and poorly differentiated tumours in Rappaport's sense of the word was

not well defined. The small-cell variant is difficult to classify as either well or poorly differentiated, while the large-cell type and tumours with many blast-like cells would generally have been classified as poorly differentiated.

The nodular lymphomas always had a cellular picture similar to that of LLD-4 and no nodular lymphoma had really normal-appearing lymphocytes within the nodules (figs. 54-58). Outside the nodules, however, lymphocytic tissue with morphologically normal cells may be seen. The degree of nodularity was variable. As pointed out by Rappaport et al. (56), transitional forms between nodular and diffuse growth are seen (figs. 53, 57). Some authors, *e.g.* Cox et al. (11) classify as nodular any case where any nodularity at all can be demonstrated. Others, such as Patchefsky et al. (54) regard partially nodular cases as diffuse lymphomas. In several of my cases the nodularity was relatively insignificant in the biopsy specimen, while necropsy revealed a predominance of nodular manifestations and the former principle was therefore applied, *i.e.*, the presence of any nodularity at all classified a case as nodular. Generally speaking, the smaller the "histiocytic" component, the poorer the demarcation of the nodules. This explains the smallness of the number of nodular lymphomas in this series, as the great majority of truly nodular tumours are of Rappaport's mixed type. It is obvious that there is no difference in kind, but only in degree between the nodular cases of lymphocytic type and such as should be classified as mixed, but since this investigation concerned leukemic manifestations of lymphocytic lymphoma, the material was limited, as described above. It should also be stressed that evident, well demarcated nodules were needed for the classification as nodular, and that the cloudiness described in LLD-4 was not regarded as nodularity. A certain degree of similar cloudiness resembling nodularity may be seen in LLD-3, but never well demarcated nodules (fig. 171).

The nodular lymphomas will not be extensively studied because of the smallness of their number. They were included for comparison with the diffuse types of lymphocytic lymphoma, however.

In the histologic classification of lymphoma, technical factors are of paramount importance. IF are difficult to demonstrate in poorly fixed tissue or in over-stained sections. Several lymphoma biopsy specimens had to be excluded from this series as no acceptable sections could be prepared from the blocks.

The material consisted of specimens from 41 cases. The distribution of the diagnoses is given in table 1. This distribution is, of course, not representative of the necropsy material because, as a rule, biopsy specimens were not obtained from clinically characteristic cases of CLL.

II. Survival data.

The figures are given to the nearest year or month. The material is summarised in table 1.

III. Extent of disease at the time of diagnosis.

The simple clinical and roentgen examinations used during the major part of the period covered by the investigation did not make it possible to grade the cases according to modern principles. The findings are given in table 2.

Diagnosis	Number, all (M/F)	Mean age at diagnosis, years	Mean age at death, years	Mean survival after diagnosis, months	Died of lymphoma	Mean survival of those who died of lymphoma, months
LLD-1	13 (10/3)	68	72	46	8/13	58
LLD-2	2 (M)	52 65	53 77	16 148	2/2	
LLD-3	7 (4/3)	58	63	58	5/7	61
LLD-4	13 (10/3)	61	65	44	12/13	47
LLN	6 (2/4)	56	60	44	6/6	44
Total	41 (28/13)					

Table 1. Lymph node biopsy series.

DIAGNOSIS NUMBER OF CASES	GENERAL EN- LARGEMENT OF PERIPHERAL LYMPH NODES	A SINGLE SITE	MORE THAN ONE SITE ABOVE DIAPHRAGM	SPLEEN PALPABLE	LIVER PALPABLE	BONE MARROW EXAMINATION POSITIVE	REMARKS
LLD-1 13	9 A	3 A	1 A	4 A	2 A	8/8 A	1 HL IN NOSE
LLD-2 2	2 $\frac{1}{1}$ A C			1 A		2/2 $\frac{1}{1}$ A C	
LLD-3 7	5 $\frac{3}{2}$ B C	2 $\frac{1}{1}$ B C		2 $\frac{1}{1}$ B C	2 $\frac{1}{1}$ B C	5/6 $\frac{4}{1}$ B C	
LLD-4 13	7 $\frac{3}{2}$ A B C	4 C	1 C	4 $\frac{3}{1}$ A C	2 A	5/8 $\frac{3}{1}$ A B C	1 TONSIL ONLY (C)
LLN E	2 C	3 $\frac{1}{2}$ B C	1 C	1 C		0/3	1 EXTRADURAL LYMPHOMA OF SPINE (C)
A	>10000 WPC >45 % LYMPHOCYTES						
B	<10000 WPC >45 % LYMPHOCYTES						
C	<10000 WPC <45 % LYMPHOCYTES						

Table 2. Extent of disease at the time of diagnosis in lymph node biopsy series.

IV. Leukemic manifestations and bone marrow findings.

The WBC and the percentage of lymphocytes in the peripheral blood at the time of diagnosis are given in table 3.

Diagnosis Number of cases	WBC > 10000 Lymphocytes > 45 %	WBC < 10000 Lymphocytes > 45 %	WBC < 10000 Lymphocytes < 45 %
LLD-1 13	13		
LLD-2 2	1		1
LLD-3 7		4	3
LLD-4 13	3	3	7
LLN 6		1	5

Table 3. WBC and percentage of lymphocytes at the time of diagnosis in lymph node biopsy series.

The leukemic manifestations in the various groups are described below.

LLD-1. The WBC varied from 11,000 to 275,000. All cases were clinically CLL. In 8 cases the bone marrow was examined at the time of diagnosis and invariably showed heavy lymphocytic infiltration. Five of the patients had immature +, 3 had ++. Of the patients with ++, 2 had also ++ in the peripheral blood, 1 had +.

Lymphocytic infiltration in the bone marrow was found in all 13 cases at necropsy. The necropsy findings are described in a later section.

The morphology of the lymphocytes in the peripheral blood in LLD-1 was never really normal, yet it was difficult to point out clearly pathological features in each individual cell. The mature cell compartment always varied somewhat in size and nuclear structure (fig. 5). Single immature cells could always be demonstrated in the blood, in 2 cases more abundantly (++). The immature cells were cytologically identical in the blood and bone marrow. They were some 50 % larger in diameter than the mature cells and had a lower nuclear/cytoplasmic ratio, and the cytoplasm showed a varying degree of basophilia. One or sometimes 2 nucleoli were seen (figs. 5, 6). The nucleus was often eccentric, round or slightly indented, and showed slight condensation of chromatin, but the cells differed distinctly from mature lymphocytes and rarely was it difficult to decide to which group a given cell belonged. These cells

correspond to the prolymphocytes described in the lymph nodes. In the bone marrow an even larger cell was sometimes, though rarely, met with. This cell had abundant, strongly basophilic cytoplasm, sometimes with vacuoles (figs. 6, 143). They were rarely seen in the blood. These cells most probably correspond to the large, immature cells described in the lymph nodes.

The cellular outfit of CLL is discussed further in chapters 8, 10 and 11.

In most patients in the group the lymphocytes in the peripheral blood were of the same size as small lymphocytes in normal persons. In 2 cases the cells were large and had fairly much cytoplasm. The mature cell content of the blood was largely the same as that in the marrow.

All the cases with a low immunoglobulin level had very few plasma cells in the bone marrow. One (600/65) had abundant plasma cells and high immunoglobulin values. Immature cells of the 2 above mentioned types were extremely sparse in this case.

LLD-2. One case (663/58) had 52,000 WBC with 99 % immature cells of prolymphocyte type (fig. 13). Examination of the bone marrow showed dense infiltration with immature +++ (fig. 12). The patient died from the disease after 16 months and then showed diffuse myelofibrosis with lymphocytic infiltration with similar cells (fig. 14).

The other patient in this group (671/66) had a normal WBC and a normal percentage of lymphocytes at the time of diagnosis but 50 % lymphocytes in the bone marrow with half of the cells mature, the other half of prolymphocytic type (fig. 17). The blood remained normal until 8 months before death, when the WBC rose abruptly to at most 54,000 with 90 % "atypical lymphocytes" (slide no longer available). The patient died 148 months after the diagnosis. Necropsy revealed diffuse bone marrow infiltration.

The majority of the cells in both cases closely resembled the prolymphocytes in LLD-1. One case (663/58) showed a strong preponderance of these cells in both the blood and the bone marrow, while the mature lymphocytes were sparse. 671/66 had about 50 % of each type of cell in the bone marrow.

LLD-3. The 3 aleukemic cases. Only 1 patient remained without atypical cells in the blood. But this patient (1140/71) only survived for 7 months. At the time of the diagnosis bone marrow examination demonstrated 30 % of lymphocytes with slightly atypical features but few with evident nucleoli (fig. 29). WBC 4,600, lymphocytes 42 %. Very rapid deterioration in spite of chemotherapy. Post mortem revealed LLD plus a malignant tumour with bizarre cells resembling Hodgkin's disease (figs. 31,32). This kind of tissue consisted of small foci in the lymphatic infiltrates and most of the nodes showed only LLD without Hodgkin's disease, as did the marrow.

One patient (855/67) had never had leukemic values, but the percentage of lymphocytes were sometimes increased with "atypical cells". The patient died of HL 137 months after diagnosis (fig. 173). The bone marrow had been normal *intra vitam* and at post mortem.

One of the patients later became leukemic (1147/65). Three years after diagnosis (without treatment) this patient still had a normal WBC, but 65 % lymphocytes. Radiotherapy was given and leukopenia with a varying but high percentage of lympho-

cytes developed. The bone marrow 70 months after the diagnosis contained 60 % lymphocytes with many atypical, but preponderantly mature cells, partly in the form of compact groups, sometimes clustered around histiocytes (figs. 26-28). 23 months before death (104 months after diagnosis) the WBC increased to at most 35,000 with 90 % atypical lymphocytes. The values became normal again after radiotherapy, but the patient died from the disease 127 months after diagnosis. The WBC was terminally normal, but necropsy revealed compact, diffuse infiltration of the bone marrow.

Of the 4 patients with normal WBC but a raised lymphocyte percentage, only 1 remained without clearly leukemic values. At the time of the diagnosis this case (1120/60) had a moderately dense, diffuse bone marrow infiltration with partly atypical lymphocytes, but with few immature cells (figs. 33-35), while the lymph node demonstrated many large, blastic forms (fig. 37). There was a clear difference between the pictures of the bone marrow and the lymph nodes. This patient never had more than 7,000 WBC, but the lymphocytes in the peripheral blood reached 95 % (fig. 36). At necropsy 7 months after diagnosis the lymph nodes showed HL (fig. 38), while the bone marrow picture was unchanged.

One case (1107/69) had at the time of diagnosis enlargement of the lymph nodes of the hilar region of the lungs, but otherwise no organ enlargement. The WBC was 10,000 with 49 % lymphocytes. Examination of the bone marrow showed sparse infiltration of small-cell type with single atypical cells with deep clefts in the nucleus and immature +. The diagnosis of lymphoma was regarded as uncertain and no treatment was given. The WBC afterwards varied spontaneously between normal and slightly leukemic values (6,000 - 14,000) without any clear tendency to rise. The lymphocytes of the peripheral blood generally comprised approximately 60 % of the WBC. 61 months after the diagnosis the patient died of myocardial infarction without having shown any clinical signs of lymphoma and without having received any treatment. The bone marrow showed focal infiltration at necropsy.

Two patients (220/72 and 705/70) developed a clearly leukemic picture.

220/72 had at the time of the diagnosis a WBC of 4,100 with 62 % lymphocytes, single atypical. The bone marrow contained 20 % lymphocytes with moderate atypia (immature +), often in small clusters. The spleen contained similar cells (fig. 39). Twenty months before death the WBC rose abruptly (from 3,600 with 44 % lymphocytes to the next examination 5 weeks later, when it was 174,000 with 93 % lymphocytes). The cells in the blood showed moderate atypia, but few immature forms. During corticosteroid therapy the WBC varied irregularly between this maximal value and 11,000. Forty months after diagnosis the patient died from chronic pyelonephritis. The WBC was finally 27,000 and the bone marrow at necropsy showed focal infiltration.

Case 705/70 had a normal WBC with 72 % lymphocytes at the time of the diagnosis. The bone marrow showed 88 % lymphocytes with a high percentage of atypical forms. Immature ++ (figs. 21-23). The peripheral blood contained mainly normal lymphocytes and only occasional atypical cells. The WBC fell to subnormal level during treatment with chlorambucil. About 1 month before death WBC rose to a leukemic level with more than 95 % atypical lymphocytes (figs. 24-25). At necropsy

27 months after diagnosis the bone marrow was densely and diffusely infiltrated.

The bone marrow finding in this group was characterised by mainly small lymphocytes with sparse cytoplasm. In all the cases the nuclei of a certain percentage of the cells were irregularly shaped and many showed deep clefts, which often resembled a line through the nucleus. The cleft was best seen in really thin sections (fig. 28). In many cells the structure of the chromatin was coarse, but there was a varying number of more immature and blast-like cells. All varieties were seen, ranging from the coarse nuclear structure to the blast-like structure, but no distinct maturity classes such as those described in LLD-1. The visibility of the nucleoli varied along a continuous scale. Very often small groups of lymphoma cells were clustered around a histiocyte.

LLD-4. Three cases were leukemic at diagnosis.

Case 397/59 had dense infiltration of the bone marrow with blast-like cells and the picture was at first interpreted as undifferentiated leukemia (fig. 64). The cells in the blood were, however, clearly lymphocytic (++) (fig. 65). The highest WBC was 99,000. At necropsy 23 months later the bone marrow was diffusely infiltrated.

Case 451/61 remained leukemic during the entire course of 27 months. The bone marrow at the time of the diagnosis had shown moderately dense infiltration with large cells of a fairly coarse nuclear structure and immature ++ (fig. 43). Cleft nuclei were less common. The cells in the blood were identical. Necropsy showed diffuse infiltration in the marrow.

Case 963/66 showed a successively rising WBC (20,000 - 60,000) with atypical lymphocytes (figs. 47, 48). The bone marrow contained 60 % lymphocytes, with preponderantly cleft nuclei and immature ++ (figs. 45, 46). The patient died from heart disease already after 5 months. Necropsy revealed diffuse infiltration of the bone marrow.

Of the 3 cases with normal WBC with a raised lymphocyte percentage, 243/73 showed no infiltration in the bone marrow at the time of diagnosis (lymphocytes 52 % in blood) and the WBC never rose to leukemic level. The patient died after 19 months. Necropsy revealed only very small focal infiltrates of lymphoma in the bone marrow.

Case 619/64 had a WBC of 10,000 with 57 % lymphocytes at diagnosis. The bone marrow showed moderate infiltration (specimen no longer available). The patient survived 32 months. No values had been noted between the diagnosis and 5 months before death, when WBC was 34,000 with 85 % atypical lymphocytes (fig. 44). The bone marrow then showed dense infiltration with atypical cells and immature +. Necropsy revealed focal infiltration of lymphoma.

486/73 had a WBC of 7,200 with 56 % lymphocytes at the time of the diagnosis. Bone marrow examination demonstrated a moderately dense, diffuse infiltration in sections. The cells were moderately atypical (immature ++). The WBC fell to sub-normal levels during radiotherapy, but the lymphocytes of the blood were consistently atypical. The patient survived for 20 months. Four months before death the WBC began to rise to a maximum of 16,700 with 87 % atypical lymphocytes. Severe thrombocytopenia and anemia developed and the patient died of a generalised zoster.

Seven cases were aleukemic at the time of the diagnosis. Two of them remained normal (1059/61 and 1047/63).

1059/61 survived only for 7 months and no specimens of the bone marrow were examined post mortem.

1047/63 survived for 15 months and had focal bone marrow infiltrates at necropsy.

Two patients later had atypical cells in the blood without clearly leukemic values. Case 737/57 always had a normal WBC and normal percentage of lymphocytes, but consistently "atypical lymphocytes" in the peripheral blood. No bone marrow examination during life.

Case 535/62 had a normal bone marrow examination at the time of diagnosis. The patient survived 93 months. One month before death 67 % "blasts" appeared in the blood when WBC were 8,300. At necropsy the bone marrow showed focal infiltrates.

Three cases later became clearly leukemic (198/57, 762/65 and 865/67).

198/57 survived 65 months. Two months before death the bone marrow aspirate (not available) was "dominated by blasts". Less than one month before death the WBC rose to a maximum of 12,200 with 29 % "lymphocytes" and 40 % "blasts". Necropsy showed diffuse infiltration of the bone marrow and osteolytic tumours.

762/65 survived 126 months. Examination of the bone marrow 60 months after the diagnosis showed no infiltration. Three months before death the WBC rose to 195,000 with 94 % "lymphocytes" (specimen no longer available). At necropsy the bone marrow was diffusely infiltrated.

865/67 survived 46 months. Two months before death she developed leukemic values with at most 106,000 WBC with 93 % "lymphoblasts". Necropsy revealed diffuse infiltration of the bone marrow.

LLN. No patient was clearly leukemic when the diagnosis was made. Only one had a raised lymphocyte percentage. This case (300/65) survived for 34 months with fluctuating values of the lymphocytes, with a maximum of 59 % atypical lymphocytes (fig. 59) at a WBC of 4,600. The bone marrow was not examined at the time of diagnosis. Necropsy revealed osteolytic bone tumours (HL).

Another patient (609/69) had normal values at the time of diagnosis and the bone marrow appeared normal. The percentage of lymphocytes afterwards fluctuated and reached a maximum of 50 % atypical lymphocytes when WBC was 7,800. The patient died 65 months after the diagnosis and the bone marrow then showed osteolytic HL-tumours.

Two patients remained normal in the blood throughout. One of them (613/66) survived only for 5 months. Necropsy showed focal infiltrates in the bone marrow. The other one (341/71) survived for 52 months. The bone marrow was normal intra vitam and at necropsy.

Two of the patients showed constant leukopenia during treatment without abnormal cells in the blood. Ten months before death one of them (219/73) had sparse bone marrow infiltrates (figs. 60 - 63) and, at necropsy, massive diffuse infiltrates with necrosis. The other, 272/73, showed no marrow infiltration intra vitam or post mortem.

The cytologic picture in LLD-4 and in LLN was very similar, and the blood cytology would not permit differentiation between LLD-4 and LLN. The picture was quite different from LLD-1 or LLD-2. The demarcation towards LLD-3 was difficult. Generally LLD-4 and LLN had more pronounced atypia but the border was unsharp and it is not possible to make a diagnosis of the lymph node histology from the blood picture. Immature lymphocytes are seen in LLD-3 as well as in LLD-4 and in all those conditions blast cells in the blood are very rare.

A summary of the leukemic manifestations is given in table 4.

Diagnosis Number of cases	Absolute lympho- cytosis during some period	Leukemic values during some period	Bone marrow infiltration Diagnosis Necropsy	
LLD-1 13	13	13	8/8	13/13
LLD-2 2	2	2	2/2	2/2
LLD-3 7	6	4	5/6	6/7
LLD-4 13	10	8	5/8	12/12
LLN 6	2	0	0/3	4/6

Table 4. Summary of leukemic manifestations in lymph node biopsy series.

V. Laboratory examinations.

The results of some measurements and tests are summarised in table 5. In some cases records of the examination in question were not available.

Immunoglobulin levels. The findings are summarised in table 6.

LLD-1. The 2 patients with high immunoglobulin values were 600/65 and 1404/67. 600/65 had even 2 years later a high value, which afterwards fell to subnormal level after the beginning of treatment. In 1404/67 electrophoresis showed signs of activity, probably because of an infected carcinoma of the urinary bladder. No control examination was performed. This group comprised 3 patients with M-components:

136/58 who also had IgG-myeloma.

DIAGNOSIS NUMBER IN GROUP	1	2	3	4
LLD-1 13	8/12	3	1/8	7/11
LLD-2 2	1/2	0	No EXAM	0/1
LLD-3 7	5/7	0	0/4	1/7
LLD-4 13	5/13	1	3/5	3/13
LLN 6	4/6	0	No EXAM	2/6

- 1: HEMOGLOBIN CONCENTRATION BELOW NORMAL LIMIT AT DIAGNOSIS (M <13,2g/100 ML. F <11,6g/100 ML)
- 2: CLINICALLY SIGNIFICANT HEMOLYSIS ON SOME OCCASION DURING COURSE
- 3: COOMBS' TEST POSITIVE ON SOME OCCASION
- 4: PLATELETS BELOW NORMAL LIMIT ($150 \times 10^3/\mu\text{L}$ AT DIAGNOSIS)

Table 5. Laboratory examinations in lymph node biopsy series.

DIAGNOSIS	NUMBER OF CASES EXAMINED	Low	NORMAL	HIGH	COMMENTS
LDD-1	11 (8)	6 (8)	3	2	ONE CASE IS EXCLUDED BECAUSE OF CONCOMITANT MYELOMA 2 CASES WITH M-COMP
LDD-2	2 (1)	(1)	1	1	
LDD-3	5 (7)	(2)	(2)	5 (3)	4 CASES WITH M-COMP
LDD-4	12 (8)	5 (4)	4 (2)	3 (2)	1 CASE WITH M-COMP
LLN	5 (4)	(1)	5 (3)		1 CASE WITH M-COMP

NUMBERS WITHIN BRACKETS ARE EXAMINATIONS LATE IN THE COURSE.

Table 6. Immunoglobulin recordings in lymph node biopsy series.

185/63 had a small Ig μ -component (0.23 gram/100 ml) in serum, also present in urine.

586/71 had a small Ig μ L in the urine (amount not determined).

LLD-2. 663/58 was examined only at the time of diagnosis. Normal immunoglobulin. 671/66 fell successively during the disease from high to low values.

LLD-3. In 1140/71 only one examination was performed and that some months before death. IgG and IgM were low. Many of these cases, however, were remarkable because of their high immunoglobulin levels and this group had the highest frequency of monoclonal immunoglobulin components.

1120/60 invariably had a low background immunoglobulin value at various examinations during the short medical history, but a rapidly growing M-component (IgGL), which increased in concentration from 0.57 gram/100 ml to 1.41 gram/100 ml in 6 months. He also had free lambda-chains in the blood. The lymph node and the bone marrow contained occasional plasma cells of normal appearance.

1147/65 had at the first electrophoretic examination 2.27 gram/100 ml diffuse immunoglobulin without signs of activity. Ten electrophoretic examinations in the course of the disease showed values between 1.74 and 3.15 gram/100 ml for immunoglobulins, mostly without signs of activity. Plasma cells were sparse in the lymph node, but abundant in the bone marrow.

855/67 had a long history with multiple organ symptoms interpreted as autoimmune disease (test for antinuclear factors positive). He had a diffuse increase of immunoglobulin already 9 years before the diagnosis, 20 years before death. At the time of diagnosis the values were around 5 gram/100 ml. After splenectomy (because of lymphoma) the values fell roughly by 50 %, but afterwards rose to reach a maximum level of 6.7 gram/100 ml. Treatment with chlorambucil was started and the values fell considerably. For about 6 months the electrophoresis showed an IgM-monoclonal component with a maximum concentration of 2.5 gram/100 ml. During corticosteroid therapy this component disappeared and during the last 5 years of his life the patient had diffuse hyper-immunoglobulinemia with values varying between 2.5 and 4.5 gram/100 ml. Eight examinations of the bone marrow during the disease had shown massive plasmocytosis, but no infiltration of the lymphoma. Lymphoma tissue in the lymph node showed occasional plasma cells. Necropsy revealed HL.

1107/69 had initially 1.73 gram/100 ml diffuse immunoglobulin, which persisted at that level at 5 electrophoretic examinations, generally without signs of activity. The lymph node contained occasional plasma cells, as did the bone marrow.

705/70 had at the time of diagnosis 1.78 gram/100 ml diffuse immunoglobulin. Two years after onset, when he was being treated, the immunoglobulin values were close to the lower limit of the normal range. The urine then contained an M-component in the form of kappa-chains in low concentration. The examination of the bone marrow at the time of diagnosis revealed 88 % atypical lymphoid cells and occasional plasma cells. The lymph node showed abundant plasma cells.

220/72 had at the time of diagnosis 2.7 gram/100 ml oligoclonal immunoglobulin. The increase persisted for about 2 years and afterwards the value became normal.

The urine contained an increased amount of kappa-chains (amount not determined). The lymph node contained abundant plasma cells, the bone marrow a normal number.

In all the cases the plasma cells of the nodes and of the marrow were morphologically normal. "Lymphoplasmacytoid" cells with an intermediate morphology between lymphocytes and plasma cells were never seen.

LLD-4. In this group there was no dominating pattern of immunoglobulin values. There was a general trend to falling values during the course of the disease, but half of the patients examined late in the course still had normal or high values. One patient (397/59) had a small monoclonal fraction in β_2 , which was not further classified or quantified.

One case (451/61) had very high levels throughout. Initially the diffuse immunoglobulins were 3.29 gram/100 ml. The value fell somewhat during treatment, but in all examinations performed the values were high and even just before death it was 2.42 gram/100 ml without any other signs of activity. The lymph node contained numerous plasma cells (fig. 42) and a very occasional large blast cell similar to those seen in LLD-3 could be found. The picture thus was somewhat dubious as to classification but as almost no normal appearing lymphocytes were present it was assigned to LLD-4.

LLN. All of the patients examined early in the course had normal immunoglobulin levels. There was a general tendency to falling levels, especially after therapy, but most of the patients examined retained a normal reactivity during infections. One patient (272/73) constantly had background immunoglobulin around the lower limit of the normal range and an M-component (IgGL) of about 1 gram/100 ml. Judging from determinations made on several occasions this concentration was constant. The lymph node contained only an occasional plasma cell. The bone marrow examination for lymphoma infiltrates at the time of the diagnosis was negative. The specimen contained 4 % plasma cells, with occasional large, nucleolated cells, but did not show a clear picture of myeloma.

Blood groups. As far as could be judged from the small figures, the distribution of ABO and Rh-blood groups was normal for the population both within the groups and in the material as a whole. This also holds for the total necropsy material.

VI. Necropsy findings.

LLD-1. In 9 of the 13 cases the histologic findings at necropsy were of the same type as those seen in the biopsy specimen. Four had HL. The 9 patients with an unchanged picture had survived, on the average, 44 months. After the exclusion of the patients who had died from some intercurrent disease the mean survival time was 58 months. The corresponding figure for the patients with HL was 51 months including the case of myeloma, excluding this case, also 58.

Generalised involvement of the lymph nodes was seen in all cases with unchanged histologic appearance of the infiltrate. But the inguinal lymph nodes were of dubious value for making a diagnosis in 3 and the axillary nodes in 1. As for IF in the necropsy specimens, see chapter 6 and chapter 8.

The bone marrow showed lymphocytic infiltration in all 13 cases. In 11, it was dense and quite diffuse. Two had focal infiltrates, where the lymphocytes had for-

med compact and frequently perfectly round foci, while the parenchyma in between showed little or no lymphocytic infiltration. In these 2 cases the WBC shortly before death were about 20,000, which were not the lowest found. After treatment with cyclophosphamide 1 case (586/71) finally had severe leukopenia with about 50 % lymphocytes, but showed dense, diffuse infiltration. After cytostatic therapy one (1107/73) finally had a normal WBC but dense, diffuse infiltration of the marrow.

One (136/58) had also multiple myeloma, diagnosed at the same time as CLL. The bone marrow showed characteristic foci, which consisted entirely of myeloma cells without lymphatic infiltration. The surrounding parenchyma exhibited diffuse lymphocytic infiltration. No extra-skeletal changes of myeloma were seen.

Two (1332/68 and 586/71) had no lesions in the liver or spleen. Both had been treated with large doses of cyclophosphamide. But the lymph nodes showed changes also in these 2 cases.

In the other 11 cases changes were seen in the liver and spleen. The weights of the spleen varied between 150 gram and 1900 gram. The mean weight in the cases with infiltration was 770 gram. The weight of the liver varied between 1340 and 2930 gram with a mean of 2030 gram. The liver infiltrates had the character of an expansion of the portal tracts sharply outlined against the parenchyma.

In 11 cases the kidneys showed microscopic lesions. They had the character of an infiltrate in the connective tissue around the vessels and especially in the cortical arteriosclerotic scars. The renal pelvis was represented in sections in 8 cases, all with lymphocytic infiltration of the fatty tissue. The lungs showed infiltration in 9 cases. The infiltration was seen around bronchi and vessels or subpleurally, mostly in the areas where there is normally lymphatic tissue and it was difficult to recognize the borderline between normal and abnormal. No tumorous infiltration was seen in any of the cases.

In one case the tonsils were enlarged and there was considerable infiltration of the testicles. One case showed heavy infiltration of the subendocardial connective tissue.

Four cases had HL in at least one organ. One of them had microscopic HL-foci in the bone marrow, the others showed only lymphatic infiltration without HL in the bone marrow. Two had HL in the spleen and 3 in the liver, while all had HL in some lymph node. HL in LLD-1 is discussed in chapter 9.

LLD-2. In both cases there was terminal leukemia. One of the patients (671/66) survived 148 months and necropsy showed generalised infiltration of the lymph nodes, spleen, liver and bone marrow with the same type of cells as in the biopsy specimen. The other (663/58) died 16 months after the diagnosis of leukemia. Necropsy showed diffuse myelofibrosis with infiltration of lymphatic cells (fig. 14). Lymph nodes, liver and spleen showed a peculiar lympho-histio-fibrocytic type of infiltration (figs. 15, 16). No extra-lymphatic tumours were seen in these two cases.

LLD-3. The necropsy findings are summarised in table 7. Four of the 7 cases had developed lethal HL. They had survived, on the average, 45 months. The corresponding figure for the other 3 cases was 76 months, but 2 died of non-lymphomatous diseases.

	Lymph nodes	Spleen	Liver	Bone marrow
All	5	6	7	Diffuse 4
Exam.				Focal 2
incom-				Normal 1
plete	2			
HL				
4 cases	3	1	2	0
Remarks		One splenecto-	Always	
		mised because	portal	
		of lymphoma	tracts	

Table 7. Necropsy findings in LLD-3 (7 cases). The figures denote number of cases with affection of the organ in question by LLD-3 or HL.

1140/71 had preponderantly lymphocytic lymphoma in all the lymph node sites. In the diffuse lymphatic infiltration there were foci of a bizarre-celled malignant tumour, which was difficult to classify (figs. 31-32). It resembled Hodgkin's disease. It was not characteristic, however, and for the sake of simplicity it is included in the table as HL.

Examination of the peripheral blood had been performed within the last few days in all of the patients except one. Five of them had a raised lymphocyte percentage with atypical cells. The sixth patient (855/67) had a massive neutrophil leukocytosis. The necropsy specimens showed HL with necrotising arteritis (figs. 173-175).

In 2 of the patients the nodal examination was not complete. One of them (1107/69) had lymphomatous nodes in the mediastinum. The other nodes were of normal size, but were not examined microscopically. The other patient with incomplete nodal examination had generally enlarged nodes.

The nodes engaged by HL were in all the cases in the mediastinal or retroperitoneal sites.

The bone marrow infiltration was generally not so dense as in LLD-1. In case 1140/71 with diffuse infiltration the pathological cells were rather sparsely distributed. The foci in cases with focal infiltration were never well demarcated.

The splenic infiltrates often had a slightly nodular appearance, but no well demarcated, follicle-like structures were ever seen. Case 220/72 had large amounts of hyaline in the spleen.

The lymphocytic infiltration of the liver was always confined to the portal tracts. The appearance was histologically identical to LLD-1, *i.e.*, expansion of the portal tracts without infiltration of the parenchyma.

No tumour formation was seen outside the lymphatic system in any of the patients in this group.

LLD-4. The necropsy findings are summarised in table 8.

LYMPH NODES		SPLEEN	LIVER	BONE MARROW	EXTRA-LYMPHATIC TUMOURS, 7 CASES	
ALL	10	DIFFUSE	10			
BOTH SIDES OF DIAPHRAGM	1	TUMOROUS	1	DIFFUSE	7	STOMACH
BUT SOME NODES	1	SPLENECTOMY	1	" + TUMOUR	1	SKIN
NORMAL	2	NORMAL	1	FOCAL	4	ADRENALS
EXAM.				NO EXAM.	1	LUNGS
INCOMPLETE	1					HEART
						PLEURA
						PANCREAS
						COLON
						APPENDIX
						OVARY
						DURA
						DIAPHRAGM
HL	1 (ALL)	HL-CASE	1	1		SOFT TISSUES OF PELVIS
1 CASE		SPLENECTO- MISED				

Table 8. Necropsy findings in LLD-4 (13 cases). The figures denote number of cases with affection of the organ in question by LLD-4 or HL.

One of the patients (451/61) had developed HL. This patient had survived for 27 months. He was leukemic during the entire course. Including this one, 8 of the patients had leukemic values at the time of death. Another 2 had atypical lymphocytes in a raised percentage and only 3 had normal numbers of WBC and lymphocytes.

Including the HL-patient, 12 died of lymphomatous disease. One died already after 5 months of myocardial infarction.

In 5 of the cases some of the tissues examined showed a histological pattern of the lymphoma, which could be suspected of nodularity, though no really well demarcated nodules were ever seen.

In 10 cases liver infiltrates were confined to the portal tracts. When small, these infiltrates could hardly be differentiated histologically from those of LLD-1 or LLD-3. When large, however, there was a tendency of infiltration into the parenchyma, which was not seen in the aforementioned groups, where the demarcation between portal tract and parenchyma was always sharp. The case with the tumour in the liver also had some slight portal tract infiltration. The group was characterised by a high percentage of cases with extra-lymphatic tumours, see table 8.

Six of the cases had diffuse infiltration of the kidneys. Five of them were leukemic at the time of death, one had a raised percentage of atypical lymphocytes. The infiltration of the kidneys differed from that in the preceding groups in that they were generally situated deeper and were most dense at the corticomedullary junction. The tumour infiltration separated the glomeruli and tubuli by wide streaks of cells, similar to what is seen in blastic leukemia.

Cytologic detail may be somewhat difficult to appreciate in necropsy specimens. In almost all the cases, however, there was in places a seemingly more immature cytology than in the biopsy specimens. This was not of HL-type, but often resembled undifferentiated lymphoma. However, as a rule, the histological type of LLD-4 was readily identified in most parts of the infiltration.

LLN. The necropsy findings are summarised in table 9.

Lymph nodes	Spleen	Liver	Bone marrow	Extra-lymphatic tumours. 5 cases	
All LLN	1 Diffuse	2 See	Diffuse	1 Pleura	4
All LLD	1 Tumorous HL	2 text	Focal	1 Stomach	2
All HL	1 Normal	2	Nodules of HL	2 Lungs	2
HL in non-irradiated	3		Aplastic	1 Skin	2
			Normal	1 Adrenal	1
				Pancreas	1
				Dura	1

Table 9. Necropsy findings in LLN (6 cases).

Four of the 6 patients had widespread HL in the necropsy specimens. They had survived, on the average, 47 months (34-65) and they all died of lymphomatous disease. The other 2 patients also died of lymphoma and survived for 5 and 70 months.

All of the patients had had involvement of all the lymph node sites on some occasion. In 3 no lymphoma was found in the peripheral nodes at necropsy, but these sites had been irradiated.

One of the patients had a tumorous HL in the liver, one had some slight lymphoma infiltration in the connective tissue of a liver cirrhosis, 4 had no infiltration of the liver. Two of the patients had tumours in the kidneys, 4 had no kidney infiltration.

Four of the patients had extra-lymphatic lesions, which were HL, one had extra-lymphatic lesions of LLD-4 type.

Four of the patients had leukopenia just before death, 2 had normal values.

VII. Natural history of some groups of lymphoma, as judged from a retrospective analysis of cases examined on various occasions, and followed up for a long time.

The duration of the symptoms reported by the patients was remarkably uniform in all the groups. Most of them reported a swelling of the lymph nodes and/or a deterioration of the general condition for 6-12 months before the examination. But there were exceptions with a long subjective or objective previous history. This holds especially for LLD-3.

LLD-3. Two of the patients in this group survived only for 7 months (1120/60 and 1140/71).

1120/60 belonged to a family with polyposis of the colon. Because of this he was checked now and then, but nothing pathological was found until 7 months before death, and then the enlarged nodes were diagnosed incidentally. As he had a generalised disease and a raised lymphocyte percentage in the peripheral blood (WBC 6,200, lymphocytes 68 %), he must reasonably have had the disease for some time, but it had been overlooked at the control examinations and he had felt quite fit. He was treated with radiotherapy and chlorambucil. One month before death very rapid deterioration with high fever and rapid enlargement of all nodes. Necropsy demonstrated HL.

In case 1140/71 enlarged nodes had been reported for "more than 1 year". She sought medical attendance 7 months before death because of a beginning deterioration of the general condition. All the nodes then were enlarged and the bone marrow showed a very slight infiltration with pathologic cells. WBC 4,600, lymphocytes 42 %. Treatment with irradiation and cytostatics was without effect and during the last 2 months of life the patient developed a severe anemia and thrombocytopenia, and bouts of high fever. She died of hyperpyrexia. Necropsy revealed a bizarre-celled tumour, most closely resembling Hodgkin's disease.

Case 220/72 reported a feeling of a lump in the abdomen for about 1 year before she sought medical attendance. She then had a huge splenomegaly and generalised lymphadenopathy and bone marrow infiltration. WBC 4,100, lymphocytes 62 %. This patient had for a long time been treated with diphenylhydantoin because of epi-

lepsy. As it has been claimed that such therapy may be causative of lymphoma, it may be mentioned that she was the only patient in this entire series treated with anti-convulsants. The patient now was treated with corticosteroids. Leukemic values appeared 20 months before death but she was in good condition until she died of an exacerbation of chronic pyelonephritis. At necropsy still LLD-3,

The other 4 patients had signs of a long lymphoma history.

Case 1147/65 was interesting because the course of the disease had been studied for 127 months. The diagnosis was made incidentally when the patient sought advice because of myalgia of the neck. Some small cervical lymph nodes were noticed and a pea-sized node was removed for study and showed the picture of lymphoma. But no malignant diagnosis was made and the blood was not examined microscopically. The patient was afterwards symptom-free for more than 3 years apart from very slowly growing cervical lymph nodes. She then returned because of gynecologic symptoms. The WBC was still normal, but with 65 % lymphocytes. The cervical lymph nodes had grown to twice the size of a pea and similar nodes had appeared in the inguinal region. Re-biopsy (38 months after the first) showed more compact infiltration, but the same cytologic picture. The diagnosis of lymphoma was now regarded as firm and all peripheral sites were irradiated. From time to time enlargement of lymph nodes appeared in different areas and was treated successfully. The patient felt well. About 5 years before death the spleen became palpable, and from then on the patient's general condition became slowly worse. Two years before death a leukemic blood picture appeared with a maximal WBC of 35,000 with 90 % lymphocytes. The WBC fell again after irradiation of the abdomen, and the last 2 years she had a normal WBC with a high percentage of lymphocytes. About 3 months before death the lymph nodes grew rapidly and the patient became cachectic. Post mortem showed a more polymorphous picture than the node biopsies, but without diagnostic lesions of HL (corresponding to the picture of "polymorphous immunocytoma", see chapter 12).

Case 855/67 was one of the longest survivors in the entire series. He survived 137 months after the diagnosis. Already 5 years before the diagnosis there was periportal lymphocyte infiltration in a liver biopsy specimen obtained because of enlargement of the liver (specimen no longer available). These infiltrates need not, however, be ascribed to lymphoma. For several years the patient had then had fluctuating enlargement of the lymph nodes in many sites. If this enlargement of the lymph nodes was due to lymphoma the survival from the first appearance of symptoms would be almost 20 years, the first 10 without specific therapy. But that patient had a remarkable clinical picture with chills and malabsorption as well as various positive serologic reactions and a massive diffuse increase of the immunoglobulins. Necropsy revealed liver cirrhosis and necrotising arteritis as well as HL. Perhaps the case should be interpreted as chronic immunopathy with a hyperactive lymphatic system eventually developing into malignant proliferation, resembling what has been described in other auto-immune conditions (see, for example, 48). At any rate, the biopsy specimen of the lymph node 137 months before death showed lymphoma. For a long time the percentage of lymphocytes was slightly increased with atypical cells

in the peripheral blood. The last 6 months the patient had deteriorated rapidly and died in a septicemia-like condition resistant to all treatment. The liver and some nodes showed HL and the HL-tissue necrotising arteritis.

Case 1107/69 reported weakness with a marked tendency to infections during the last 2 years before the diagnosis. During this time the E.S.R. had for some unknown reason been raised. After the diagnosis the patient survived 61 months, during which his disease was dominated by a tendency to infections and fatigue, but he had no local symptoms apart from enlargement of the mediastinal lymph nodes. The WBC fluctuated irregularly between normal and 14,000 with about 60 % lymphocytes. No treatment was given. He died from myocardial infarction. The findings at necropsy showed the same histologic picture as the lymph node biopsy specimen.

Case 705/70 reported enlargement of the cervical lymph nodes for 5 years before the diagnosis, but his general condition had been unaffected. He survived 27 months after the diagnosis. One month before death leukemia appeared. During the last 4 months of life he deteriorated rapidly and the mediastinal lymph nodes grew considerably at X-ray examinations. Necropsy showed HL in them, while the other infiltrates had the picture of LLD-3.

It thus appears that the patients in this group may have their lymphoma for a very long time without effects on the general health. Also the growth of the nodes may be very slow. It appears probable that the patients may have their disease for a long time without seeking medical advice. Both of the patients who survived for only 7 months died of HL. It is not unreasonable to assume that they had had asymptomatic LLD-3 for a long time before that. Two of the other patients who did not survive so long died of some disease other than lymphoma. Much suggests that the natural history of this type of lymphoma is at least 10 years.

Judging from the above findings, the course of the disease is roughly as follows.

After a probably long aleukemic pre-stage the percentage of lymphocytes in the peripheral blood gradually increases, in the beginning without having any notable effect on the WBC. During this phase enlargement of the organs may be only mild and escape notice by the patient. The bone marrow shows sparse infiltration. This stage often lasts for several years (in 1107/69 the bone marrow examined at necropsy 5 years after diagnosis was still only sparsely affected). The WBC and the percentage of lymphocytes show a gradually increasing tendency, but the values fluctuate spontaneously and vary between mildly leukemic and normal. The cells in the blood have the same appearance as in the tissue infiltrates with the exception that only a small percentage of the blast cells leave the tissue. The percentage of immature cells is generally lower in the marrow than in the affected nodes. The atypia of the cells in the blood is by no means always striking and can be readily missed by an inexperienced examiner. Gradually the bone marrow infiltrate becomes denser and the cellular picture is dominated by tumour cells (1147/65: 57 months ante mortem, 705/70 at diagnosis, 27 months ante mortem). A critical level is reached when an increasing number of tumour cells are rather suddenly released into the blood. This is not necessarily combined with a clear clinical deterioration, but it is a sign that the disease is approaching its final phase. The duration of the clearly leukemic phase was 23 months in 1147/65 and 20 months in 220/72. 705/70 died already 1 month after

the appearance of the leukemia, but in that case HL developed in the mediastinal lymphomas.

The leukemic phase may thus last for more than 2 years. During this phase the clinical picture and the blood picture resembles CLL. In a fairly high percentage of the cases the disease changes its biologic character and HL supervenes. The patient then soon dies. HL probably always starts in the lymph nodes and is not often seen in the bone marrow. Possibly the development of HL and the development of a leukemic blood picture are unrelated phenomena, the first taking place in the lymph nodes, the second being related to the state of the bone marrow.

LLD-4. Most of the cases in this group reported symptoms for less than 12 months before diagnosis. Two patients (762/65 and 963/66) had signs of a long history, however. It is noteworthy that the lymph node biopsy specimens from these two cases were those with the smallest percentage of blast cells in LLD-4. In both of them the blasts had to be searched for carefully before found.

Case 762/65 sought medical advice because of gynecologic symptoms 126 months before death. Examination then revealed enlargement of an inguinal lymph node, which microscopically proved to be lymphoma. But the clinician doubted the diagnosis and no treatment was given. The patient afterwards felt quite well for 5 years, although the inguinal lymph nodes gradually grew in size. She was then operated upon because of ileus (adhesions). The abdominal lymph nodes appeared to be normal as did the liver and spleen. She afterwards felt well apart from gradual enlargement of the inguinal nodes for more than 3 years, after which there was an accelerated enlargement of the nodes and the liver and spleen became enlarged. The blood picture was still normal, but her general condition now deteriorated. Biopsy of a lymph node (111 months after the first) showed the same cellular picture. Radiotherapy of the peripheral sites was given and leukopenia developed, which about half a year before death was followed by increasing WBC and about 3 months before death leukemic values appeared, reaching a maximum of 194,000 with 94 % "lymphocytes". At necropsy the infiltrates were of unchanged histologic appearance. The disease was thus diagnosed incidentally more than 10 years before death. For 8 years the patient had been symptomfree, after which signs of dissemination and clinical disease appeared. During the first 8 years the enlargement of the lymph nodes was so insignificant that the patient might very well have not noticed it.

Case 963/66 was in an infirmary because of weakness due to old age. Certain routine laboratory studies were made there. Eight years before the diagnosis the WBC had been normal and the lymphocytes (55 %) slightly increased. Three years before the diagnosis he had slightly increased WBC, 12,000, with 55 % lymphocytes, and mild trombocytopenia, 90,000/ μ l. Four months before the diagnosis the WBC had been normal (no differential count) and at the time of the diagnosis the WBC was 21,000 with 89 % lymphocytes. The patient died 5 months after diagnosis of leukemia. It is, of course, not possible to know with certainty whether these mild hematologic abnormalities had anything to do with his terminal lymphoma, but in view of the history of case 762/65, reported above, it does not appear unreasonable to assume that they had.

These two cases with very few blast cells in the nodes possibly represent a special form of LLD-4 with a more prolonged early course, but the cases were too few to separate as a special group, and the general appearance of the nodes was so similar that they were grouped together with other cases of LLD-4.

The history of 451/61 is also given because this case had many similarities to LLD-3.

The patient reported about 6 months' disease before the diagnosis. He was then leukemic. Twelve months later a new lymph node was examined and showed the same picture. Fourteen months later he died, and the lymph node site which was biopsied last showed exclusively HL, which thus must have developed within about a year. The lymph node biopsy specimens were undoubtedly of type LLD-4, but the tissue contained a very occasional cell similar to the large immature ones of LLD-3. Also, large amounts of morphologically normal plasma cells were seen. The HL tissue in the necropsy specimens was very similar to that of cases of LLD-1 or LLD-3, see chapter 9. It may be that transitional forms between LLD-3 and LLD-4 exist.

Several of the other cases of LLD-4 had been in hospital for other diseases for varying times before the diagnosis of lymphoma. Nothing in the records indicated any abnormality of the lymphatic system or of the blood during these stays in hospital.

LLN. Two of the patients had a long pre-clinical history (300/65 and 609/69). These two cases had the most pronounced nodularity and likewise the most prominent histiocytic component in the nodules of all patients in the series. Both patients died from HL.

300/65 survived 34 months after diagnosis, but reported growth of the circumference of the neck "for many years". The patient had a fluctuating, generally increased percentage of atypical lymphocytes in the blood. Already 14 months after diagnosis biopsy showed development into HL. A further 18 months later re-biopsy demonstrated diffuse HL. Twelve months later necropsy revealed generalised HL. The transition to HL thus presumably began about 2 years before death.

609/69 survived for 65 months after the diagnosis, but had noticed an increase in the circumference of the neck for 4 years. About 2 years before death atypical lymphocytosis began to appear, but the values were never leukemic. Re-biopsy after 30 and 33 months showed an unchanged picture, but after a further 30 months a tumour appeared in the gingiva. It was pure HL. The patient became rapidly worse and within a month he died from generalised HL.

Patients with LLD-1, who developed HL are discussed in chapter 9.

Some case histories are summarised in fig. II. The 2 cases with very few blasts are presented at top in LLD-4. A rough estimation of the mean survival after first symptom or sign would be 80 months for LLD-3 and 55 months for LLD-4 (the two cases with very few blasts 120 months, the others 45 months) and for LLN 50 months.

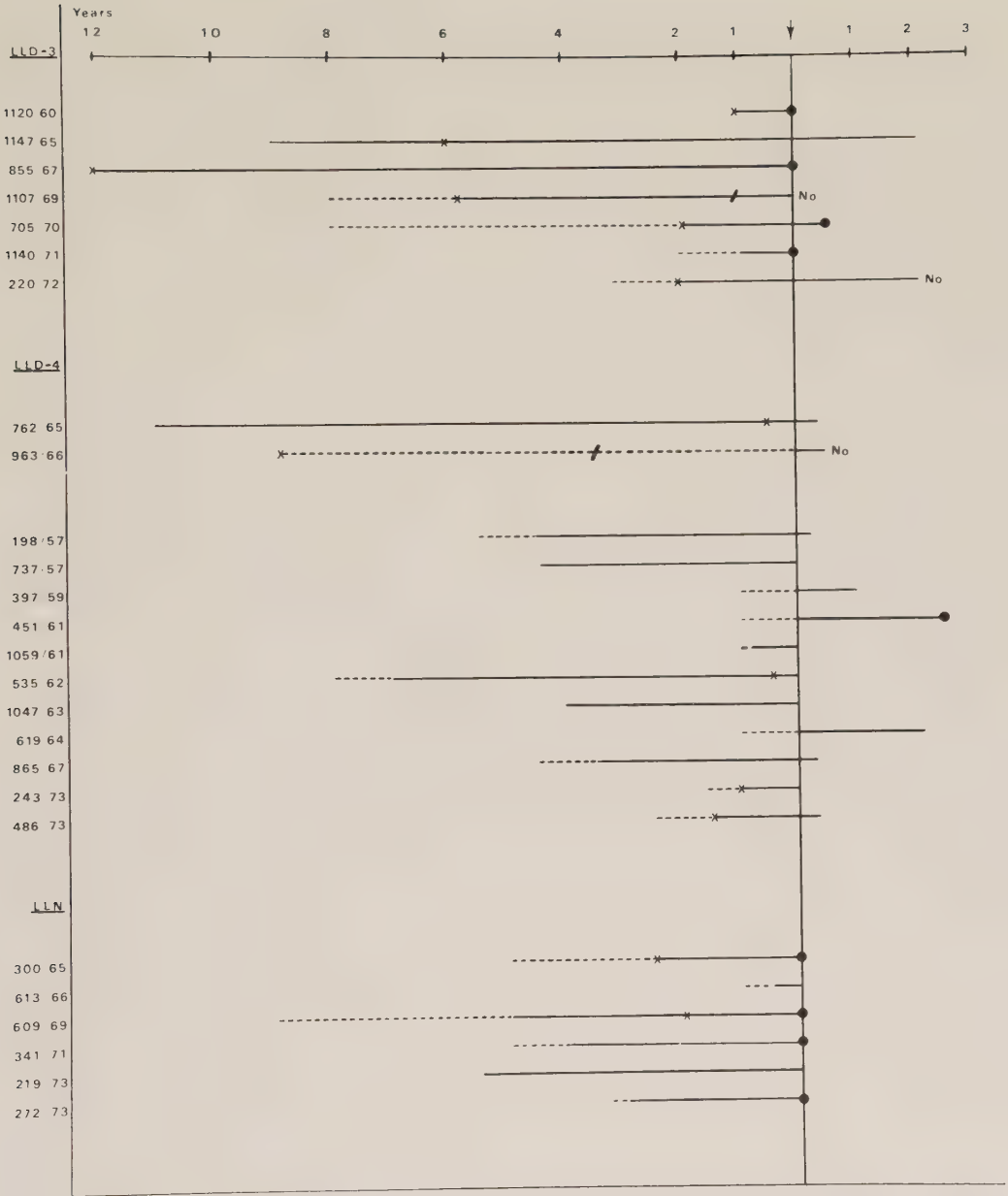


Fig. II. Summary of case histories in LLD-3, LLD-4 and LLN.

Line represents course from diagnosis to death. Non-leukemic phase to the left of the vertical line, continuous leukemic phase to the right of this line.

---- Prediagnostic phase with symptoms or signs probably due to lymphoma.

x First recording of more than 45 % lymphocytes in differential count.

/ First recording of WBC more than 10,000 with more than 45 % lymphocytes.

● HL in necropsy specimens.

No Death due to some disease other than lymphoma.

VIII. Discussion of biopsy specimens of the lymph nodes.

The smallness of the groups makes it difficult to evaluate the relevance of the classification, as no statistical differences were found owing to the wide variation of the observations. Larger series of malignant diseases of the lymph nodes have been published. The present material is presented primarily to permit comparison of the aleukemic lymphoma groups with the CLL-material. It is, of course, a limitation that the material consisted only of patients who had died, because it may result in an erroneous impression of the effect of recent developments in treatment. During a major part of the investigation period, treatment with modern drastic radiotherapeutic and cytostatic methods was not in use, and therefore the series may perhaps give a more correct picture of the natural history of the diseases. The survival rates do not, of course, hold for the situation to-day.

The range of variation of individual variables must be wide in any series where the diseases were diagnosed at different intervals after their true onset. It might therefore be difficult to demonstrate numerically significant differences even between apparently different processes. In the present investigation attempts were made to reconstruct the course from the onset of symptoms, but laboratory tests during the preclinical and polyclinical phases were sporadic, for which reason interpolation was often necessary. The groups are too small for meaningful statistical comparison of survival dates and laboratory values.

Many investigations have shown the clinical significance of Rappaport's "differentiation" of the lymphocytic lymphomas, at least regarding survival. The differentiation concept was not used here because of a desire to replace the term by two others, describing different variables. Moreover, I also found it difficult to place in Rappaport's system the tumours, which I called LLD-3 and small-cell cases of LLD-4. Rather than introducing a term such as intermediate differentiation, I decided to use the more neutral numerical designations described.

LLD-1 appeared to be the characteristic picture of the lymph nodes in CLL. All the patients were leukemic and all examined had bone marrow infiltration at the time of diagnosis. General enlargement of the palpable nodes was the rule. Exceptions were seen, but it is well known among pathologists that infiltration might exist in normal or almost normal-sized nodes in CLL and also that the liver and spleen need not be markedly enlarged in spite of infiltration. This lymph node picture probably always represents a systemic disease involving practically all lymphatic tissues from the very beginning. If an initial aleukemic stage exists, it is often not possible to diagnose it histologically, because typical lesions are seldom seen in untreated aleukemic patients at necropsy or in surgical specimens.

LLD-2 may appear to be very different on superficial examination. Few mature lymphocytes were seen, while such cells dominated the picture of LLD-1. On the other hand, all the cellular components of LLD-2 were also found in the IF of LLD-1. Cases of LLD-1 with very large IF sometimes had portions with confluent IF and thus a picture with transitions to LLD-2. Such nodes should, according to Rappaport, be classified as partly well, partly poorly differentiated. Still, the patient may have ordinary CLL from a hematologic point of view.

The two cases of LLD-2 differed from one another clinically, but both were generalised initially. One was leukemic, the other non-leukemic. As in LLD-1 two generations of cells were readily recognized in the bone marrow. The ratio between mature and immature cells was the reverse. LLD-2 presumably corresponds to the condition which Galton et al. called prolymphocytic leukemia, a term also used for other conditions (19). These authors described, under the name prolymphocytic leukemia, a rare form of lymphatic leukemia in adults. They felt that one should distinguish this disease from chronic and acute lymphatic leukemia and from chronic and acute lymphosarcoma cell leukemia. No biopsies of the lymph nodes were obtained in their cases and the description of the findings at necropsy was incomplete. The cases were characterised by less prominent enlargement of the lymph nodes, but marked hepatosplenomegaly and very high lymphocyte values in the blood. The morphologic appearance of the blood and bone marrow is described in a way corresponding to my cases of LLD-2. Galton et al. felt that the disease had a poor prognosis but they found signs of a possible long inapparent stage before the condition was diagnosed. LLD-2 thus seems to be the tissue manifestation of prolymphocytic leukemia. In Rappaport's classification, LLD-2 must be assigned to the poorly differentiated, diffuse lymphocytic lymphoma group.

LLD-3 was the most polymorphous group. Histologically, it had some similarities to both LLD-1 and LLD-4. On superficial examination it is easy to confuse the picture with LLD-1 because of the predominance of small lymphocytic cells. If are not present, however, and on careful scrutiny it was apparent even in histological sections that the lymphocytes had a greater variability than in LLD-1 and that many atypical forms were present. This trait was better appreciated cytologically in smears. Immature cells similar to those of LLD-1 and LLD-2 were present, but often the general polymorphism and atypia with nucleolated forms of lymphocytes obscured the difference between the immature and mature components in smears, and the generations were not so easily appreciated as in LLD-1. Clinically, the cases appeared to be very dissimilar with a great range in the variation of survival and "acuteness". As has been argued, however, it does not appear unreasonable to assume that the patients with a short survival had had the disease for a long time before it was diagnosed. Many cases had an extremely long survival with very few symptoms and signs and it appears probable that this kind of lymphoma has the best prognosis of those dealt with here.

From a hematologic point of view, the most characteristic findings for a great part of the course appeared to be slight bone marrow infiltration and a blood picture with normal or slightly raised WBC and a raised lymphocyte percentage, and the occurrence in the blood of atypical lymphocytes but a preponderance of normal or almost normal forms. The large immature cells of the lymphatic tissue were found only in very low numbers in the bone marrow and hardly at all in the blood. It appears probable that every case will sooner or later have a raised lymphocyte percentage. Only in one case was the percentage not raised. This case (1140/71), however, had lymphocytes close to the upper limit of the normal range at diagnosis and then survived for only 7 months and was treated intensely with cytostatics and irradiation. More than half of the cases had leukemic values at some time and in this phase the

disease closely resembled CLL, but the lymph node picture did not become that of LLD-1, and to a trained observer the blood and bone marrow pictures were different. The leukemic phase may last for several years.

The great majority of cases appeared as a systemic disease from the beginning, but exceptions were seen without general enlargement of nodes or bone marrow infiltration. As to the last, however, it may be difficult to exclude it as it may be very slight and often focal. Smears alone are not enough for the examination, but probably occasional small foci can be missed also in sections. This may apply also to necropsy specimens unless many sections are examined. In one of the cases no bone marrow infiltration was ever diagnosed, but atypical cells appeared in the blood now and then so it appears improbable that the marrow was spared. But in spite of the long survival of the patient the bone marrow infiltration, if any, must have been very slight. In no case was it proved at necropsy that unaffected nodes were present, but in one microscopically incompletely examined case there were normal-sized nodes in some sites, so it may be that the process remains confined to a single lymph node group in occasional cases. However, this case also had bone marrow infiltration. Liver and spleen became engaged in all cases sooner or later.

A large percentage of the cases developed HL terminally. This is probably the reason why so few cases with this lymph node picture are seen in necropsy specimens (see chapter 6). Many patients probably live with LLD-3 for a considerable time before they seek medical advice, or die without a clinical diagnosis when HL appears. The picture of HL may be found in some organs but LLD-3 in the bone marrow (see chapter 6), which argues in favour of this view.

The immunoglobulin values require comments. All the cases of LLD-3 examined early in the course had high, diffuse immunoglobulin levels. A varying amount of apparently normal plasma cells were found in the nodes in all cases. This contrasts with what is the rule in LLD-1. However, the plasma cells also occurred in the bone marrow, and without evident correlation with the existence or the degree of lymphoma infiltration. Because of this, and in view of the polyclonal increase, it does not appear probable that the plasma cells are an integral part of the tumour proliferation, but a concomitant phenomenon, possibly due to a reaction to the tumour, as most cases had an increased value of immunoglobulins also without other inflammatory signs in the electrophoretic pattern. Many cases also had a monoclonal component, however, which was possibly a product of the tumour cells.

In contrast to the above mentioned groups, LLD-4 often appeared to have a localised stage initially. Roughly half of the patients had only one site or organ affected at the time of diagnosis and even at necropsy the dissemination was sometimes not complete. But in the majority of cases the bone marrow was sooner or later involved, diffusely or focally. In most cases also atypical cells were released to the blood, but initially the blood picture was most often normal. A high percentage had leukemic values, but generally only for the last few months before death. Yet 2 cases were leukemic during the entire clinical course of about 2 years. Thus, from a hematologic point of view the course is rather variable. Also, the immunoglobulin pattern was less consistent than in LLD-1 or LLD-3 and high, normal or low values were seen, but in the late phases low values were most common, possibly due partly to treatment.

Monoclonal immunoglobulin components may be seen, but not so often as in LLD-3.

The few nodular lymphocytic lymphomas appeared to be localised in a higher percentage than any of the diffuse groups. Also the blood picture was generally normal at diagnosis. Atypical cells appeared in the blood in some cases, however, but clearly leukemic values were not seen. But leukemia may be seen, judging from the literature (64) and also from personal experience with similar cases not included in this study. The frequency is generally given as about 25 % of all cases of nodular lymphomas (64). But LLD-4 sooner or later developed leukemia in about 60 % in this series. The bone marrow was often involved at necropsy in LLN, but it was often a question of HL changes. The development of HL was more common in this group than in LLD-4, which did not seem remarkable as the content of "histiocytic" cells in LLN generally was higher than in LLD-4. But the picture of LLD-4 was sometimes seen mixed with that of LLN, both in biopsy and necropsy specimens, so it appears certain that they are diffuse and nodular variants of the same process. A high percentage of extra-lymphatic tumours were seen in both groups, in contrast to LLD-1, LLD-2 and LLD-3. The immunoglobulin values of LLN were generally normal in the early stages, but monoclonal immunoglobulin components may be found also in this group. They generally seem to be of type IgG (49).

Summarising, the lymphocytic diseases in question could be separated in two groups: LLD-1 and -2, which from the very beginning appear as systemic diseases, and LLD-4 and LLN, which probably in the majority of cases have a localised stage. LLD-3 appears to have an intermediate position. Most cases are probably systemic from the beginning, but the degree of bone marrow infiltration is often slight. In occasional cases, the bone marrow is spared and also some lymph node groups may not be involved. LLD-1 and -2 could be called the lymphocytic leukemias proper and LLD-4 and LLN the lymphocytic malignant lymphomas proper, but LLD-3 is not easily classified as either leukemia or lymphoma and this separation appears to be of little use as the lymphomas may be leukemic and the leukemias (at least LLD-2) may be non-leukemic. In Rappaport's classification, LLD-1 would correspond to well differentiated, diffuse lymphocytic malignant lymphoma. Possibly also LLD-3 and small-celled cases of LLD-4 with few blast cells would be assigned to the well differentiated group. LLD-2 and the rest of the cases of LLD-4 would be classified as poorly differentiated. All the nodular cases in this series would be classified as poorly differentiated.

Occasional cases appeared to have traits of both LLD-3 and LLD-4 and the border between the two groups is possibly not quite sharp.

LLD-1 is the morphologic manifestation of CLL and can generally be distinguished from leukemic lymphoma of other types. This conception argues against the conventional opinion that CLL is indistinguishable from well differentiated, aleukemic lymphocytic lymphoma. LLD-1 in the aleukemic form must be rare. There may be cases with morphological features intermediate between LLD-1 and LLD-3 (see later), but a case with an initial picture characteristic of one group does not develop a picture characteristic of the other. LLD-3 may have a long leukemic course, which is clinically difficult to distinguish from CLL. One might, of course, call this a variant of CLL, but the diseases appear to be different if one has a possibility

to follow them throughout their course.

LLD-2 is a small group more closely related to LLD-1 than to other groups of "poorly differentiated lymphoma".

The nodular lymphomas have a tendency to progress towards diffuse growth. Whether this is a prognostically bad sign is not possible to decide from this small material. The lymphoma group also has a tendency to develop into HL. This may be seen more often with the nodular variants. LLD-1 and LLD-3 often assume a more immature cytologic picture, though not that of the lymphoma group proper, but that of HL or Hodgkin's disease (see chapter 9). It is probable that LLD-1 can also undergo transformation to LLD-2 (see chapter 6).

As to the leukemic manifestations of the lymphoma group proper, it appears probable that it is a consequence of heavy bone marrow infiltration. However, atypical cells may be seen in the blood with only slight and focal bone marrow infiltration, and this also applies to LLD-3. The bone marrow picture in the leukemic phase of the lymphoma group proper may be quite immature. One might discuss the possibility that the patients had developed a new disease, a leukemia unrelated to lymphoma, e.g., caused by treatment. Such a possibility is remote because preterminal leukemia is relatively common in this category, while other cases of malignant diseases treated with similar methods rarely develop leukemia. There may be some cases in this lymphoma group that develop the picture of undifferentiated lymphoma.

Chapter 5

A STUDY OF BONE MARROW SMEARS INTERPRETED AS LYMPHOCYTIC LYMPHOMA AND LYMPHATIC LEUKEMIA

Technically acceptable smears were available in 79 cases. (The case with CLL + myeloma was excluded from this part because of the special bone marrow picture). Histologic examination of the bone marrow and special examinations such as PAS-staining and enzyme cytochemical studies were performed only during the last years and will not be dwelt on here. The classification is thus based on routine smears stained with the May-Grünwald-Giemsa stain.

The bone marrow and blood smears were examined without knowledge of the final diagnosis. It proved extremely difficult to distinguish the pictures of LLD-3, LLD-4 and LLN. Further, this material contained some cases in which necropsy or lymph node biopsy specimens exhibited a picture of undifferentiated lymphoma, but where the bone marrow picture was clearly lymphocytic and easily confused with that of LLD-3 or LLD-4. It appears doubtful whether it is meaningful to try to differentiate between these groups by the picture of the bone marrow. The cytologic picture gave no reason to suspect nodular growth. The findings in the "non-leukemia group" will be discussed later but the cases were pooled in one group.

It was suspected that a case might be of type LLD-2 if the smear contained lymphocytic cells, more than 50 % of which were clearly nucleolated and if their appearance corresponded to that of prolymphocytes, as described for group LLD-2 above. The bone marrow smears were accordingly divided into 6 groups.

1:	corresponding to LLD-1 (see chapter 4)	42 cases
2:	corresponding to LLD-2 (see above)	10 "
3:	cases judged as lymphocytic malignant lymphoma of non-leukemia type (see above)	17 "
4:	corresponding to the classical description of Waldenström's macroglobulinemia (see chapter 1)	5 "
5:	unclassifiable in this scheme	1 "
1-3:	doubtful whether group 1 or group 3	4 "

GROUP 1 .

This group consisted of bone marrow smears from 42 patients. 27 of the patients were men, 15 were women. The average age at the time of death was 75 years for the men and 77 for the women. The clinical diagnosis was CLL in 42 cases.

Of the men, 18 died from their basic disease or some complication of it. Four had HL and 1 Hodgkin's disease at necropsy. The average survival time after the diagnosis of these 18 men was 53 months.

Of the women, 9 died from their basic disease and a further 2 from miliary

tuberculosis. These 2 had well controlled leukemia and the tuberculosis should perhaps be regarded as a complication of the treatment. Of the 9, three had HL at necropsy. The average survival time of these 9 women was 66 months. The average survival time of the men + women who died from the disease was 57 months, thus practically the same figure as for LLD-1 in the lymph node material.

Of all 42 patients, necropsy demonstrated HL in 7 and Hodgkin's disease in one. The average survival time of these 8 was 67 months (30 - 180).

One patient (31/67), who died from Hodgkin's disease, reported that a twin brother and a maternal aunt had died from leukemia, but these cases could not be traced to control the correctness of the information given. There was no known blood relationship between any patients in the series.

The WBC at the time of diagnosis ranged between 10,900 with 70 % lymphocytes and 453,000. Some data are summarised in table 10.

AT DIAGNOSIS

WBC $\times 10^3/\mu\text{L}$, 42 CASES

< 100 50 %

100-200 25 %

> 200 25 %

10-20 15 %

HEMOGLOBIN CONCENTRATION

BELOW NORMAL LIMIT 25/40

THROMBOCYTOPENIA 15/30

COOMBS' TEST POSITIVE 7/28

GENERAL ENLARGEMENT OF
PERIPHERAL NODES 24/42

NO PALPABLE NODES 10/42

SPLEEN PALPABLE 18/42

LIVER PALPABLE 14/42

NO PALPABLE ENLARGEMENT
OF ANY ORGAN 10/42

MAXIMAL VALUE OF WBC
DURING COURSE, $\times 10^3$

≤ 50 23,8 %

51-100 23,8 %

101-150 9,5 %

151-200 9,5 %

201-500 26,3 %

> 500 7,1 %

MAXIMAL VALUE IN SERIES:
1238 $\times 10^3$

SIGNIFICANT HEMOLYTIC
ANEMIA ON SOME OCCASION 4/42

Table 10. Group 1 of bone marrow series.

The immunoglobulin values are included in table 14. Seven patients had on some occasion had small M-components: 4 had an IgM-component in the plasma. The light chain was determined in 2, 1 kappa and 1 lambda. The component was not quantified in 1 case, in the other 3 it had values between 0.23 and 0.30 gram/100 ml. One case had an M-component in a concentration of 0.30 gram/100 ml in β 2; it was not typed further. Two cases had Ig μ L in the urine (amount not measured). Thus, all these components were probably of an IgM-type. The 2 M-components in group 1-3 were both IgGK.

The 7 patients with M-components survived, on the average, 67 months, thus, if anything, longer than the group as a whole. Two of the HL-cases and the case of Hodgkin's disease had M-components, thus about 1 out of every 3 in the group and about 1 out of every 9 of those that did not develop HL or Hodgkin's disease. The average age of the patients with M-components at the time of death was 68 years, thus below average, arguing against the M-components being incidental to old age. A further discussion of the relation of monoclonal immunoglobulin components and HL is given in chapter 9.

Two patients had high diffuse immunoglobulin values late in the disease. They had high values also early, and both had shown signs of high activity in the electrophoretic patterns. Two others had terminally extremely low immunoglobulin values, 0.12 and 0.06 gram/100 ml.

Cytologically there were 10 cases of large-cell, mature type in the bone marrow and 32 with small-cell, mature type. Of the HL-cases, 2 belonged to the large-cell group, 5 to the small-cell group. In the case of Hodgkin's disease, the cells were small.

One patient (immature +) had crystalline inclusions in the cytoplasm (low immunoglobulin level without M-component). Seven had immature cells ++ in the bone marrow, and of these, 5 also in the blood ++, while 2 had +. Blood smears were available in a further 21 cases. They had immature cells +. Of the 7 cases with ++ in the marrow, 2 developed HL, while 5 HL-cases and the case with Hodgkin's disease had bone marrow with immature +. HL was thus somewhat more common in the ++ group than in the + group, but the figures were too small to show any significance.

Intensely basophilic cytoplasm was found in 10 cases. Except for this the cells were not of plasmacytoid appearance, but in those cases the cytologic picture was generally more polymorphous than in others in the group, though still evidently different from group 3. Two of them developed HL. Three of the 7 cases with M-components were included among these 10 (M-components were thus roughly 3 times as common among these cases as in the rest of the group).

There were thus no characteristics of bone marrow or blood picture to make it possible to predict with certainty whether the patient would develop HL or Hodgkin's disease.

NECROPSY FINDINGS. Apart from the 8 cases with HL or Hodgkin's disease, the findings in the remaining 34 cases were of the type described earlier as LLD-1. Generalised involvement of the lymph nodes was seen in 26 cases. One case was without diagnostic changes, the other 7 had 1 or 2 lymph node sites without dia-

gnostic changes, always either inguinal or axillary. The liver showed infiltration in 30 of 34 cases. The largest liver weighed 4,050 g. Microscopically the spleen had infiltrates in 30 of 34 cases. Four of the spleens involved were of normal size (weight < 200 g), only 2 weighed more than 1,000 g (max. 3,100 g). Twenty-four thus weighed between 200 and 1,000 g. The bone marrow was diffusely involved in 24 cases, focally in 6. One case was aplastic, 1 was not examined. Two had no diagnostic bone marrow infiltration at necropsy. They were hematologically normalised by therapy before death.

Some cases showed tumorous lesions outside the lymph nodes. In one case the spleen contained a tumour-like grey-white nodule, the size of a walnut. WBC terminally 90,000. In another case the liver showed multiple, pea-sized, grey-white nodules. WBC terminally 225,000.

Two cases had tumour-like lesions outside the lymphatic system. One of them (352/73) had several fist-sized, soft tissue infiltrates in the retroperitoneum and in the renal adipose capsule. They were grey-brown and very soft. WBC terminally 370,000. One case (614/67) had a tumour-like, white infiltrate about 1 cm thick under the pleura and dura. WBC terminally 216,000. In these cases the infiltrates consisted of the same type of lymphocytes as other infiltrates, and thus showed no direct signs of sarcomatous transformation. No IF were seen. Such extra-lymphatic lymphocytic tumours without signs of HL appeared to be rare and probably occurred late in patients with a high WBC.

The patient with the tumour in the spleen had also heavy diffuse infiltration in the corpus and cervix uteri, which had produced a large palpable pelvic mass and profuse bleedings. The changes had clinically been interpreted as probably cervical carcinoma. Otherwise this group contained no cases with notable organ enlargement (except the liver, spleen and lymph nodes) because of lymphocyte infiltration.

As for HL-changes, see chapter 9.

Broadly speaking, the findings in this group confirm those in the smaller LLD-1-material of node biopsies. When the disease with this cytologic picture reaches clinical significance it is probably practically always leukemic. The terminal development of HL was common also in cases with this cytologic bone marrow picture.

GROUP 2.

Of the 10 cases, only 663/58 had immature +++ in the peripheral blood. 671/66 had no lymphocytosis at the time of diagnosis, but finally became leukemic; however, no blood smears were available from that phase. Of the others, 4 had immature ++ in the peripheral blood, while 4 had immature +. The blood picture in these 4 was of ordinary type for a mature CLL (figs. 18 - 19).

It thus appears as if the bone marrow picture of type 2 may be associated with the blood picture of type 1. This must be regarded as arguing for the assumption that both are variants of the same process. Are there, then, any deviating features common to cases with a high percentage of immature cells in the bone marrow? The 10 cases in group 2 are treated here together regardless of the blood picture. See also chapter 8 on immature cells.

Six were men and 4 were women. The average age at the time of death was 74

years (53 - 92). Two had died from non-lymphoma disease. The average survival time for the remaining 8 was 48 months, thus somewhat shorter than in group 1, but the variation was wide (2 - 148). The WBC at the time of the diagnosis was normal in 1 case (4,200 with 37 % lymphocytes). The other cases had leukemic values ranging between 15,300 and 500,000. Only 2 of the patients had more than 100,000 at the time of diagnosis. In nearly all, however, the WBC reached a very high level some time during the period of illness. Six had on some occasion more than 150,000, 4 more than 200,000. In one there was only 1 initial value, 15,300, after which the patient survived a further 12 months, but the course of the WBC is not known. 671/66 became leukemic about 8 months before death, and the WBC rose to at most 54,000.

Six had hemoglobin values below the lower border of the normal range at the time of diagnosis. Two had abnormally high values, 16.3 and 20.4 gram/100 ml. The patient with 20.4 gram/100 ml had had polycythemia vera for 7 years by the time the leukemia appeared and had repeatedly been treated with P³². Coombs' test was performed in 6 cases and proved positive in 3. Significant hemolytic anemia was found on some occasion in 4 cases. Thrombocytopenia was noted at the diagnosis in 2 cases.

The immunoglobulin values are given in table 14. One M-component was found in the group (IgM).

Five of the patients had at the time of diagnosis severe splenomegaly, 1 had moderate splenomegaly. In 4 the spleen was not palpable. Four had severe generalised enlargement of the lymph nodes; in the others the enlargement was slight.

NECROPSY FINDINGS. In 8 all the lymph nodes were involved, 2 had no diagnostic changes. The liver and spleen were involved in all. The average weight of the spleen was 770 g (1 excluded because the spleen was scarred after infarction). The average liver weight was 1,740 g. The figures are not significantly above those in group 1. The bone marrow showed diffuse lymphocytic infiltration in 7. The remaining 3 (1320/64, 655/63 and 663/58) showed myelofibrosis with diffuse lymphocytic infiltration. The lymph nodes in these 3 also showed fibrosing features as well as infiltration of histiocytes without malignant morphologic traits. 655/63 had stratified fibrous nodules in the lymph nodes with a zone of polymorphous HL-like tissue in the periphery. One lymph node showed a focus of clear-cut HL (see chapter 9).

663/68 had in the beginning of the disease a slightly increased hemoglobin value and had for some time had an unexplained mild increase of the WBC with a normal differential count. 1226/65 had for a long time had polycythemia vera. Another case had pernicious anemia.

In no respect did the group show any significant clinical differences from the mature CLL-cases assigned to group 1.

The most remarkable are the 3 cases with myelofibrosis and fibrohistiocytic lesions in the lymph nodes. One might wonder whether this was due to a tendency to cellular death that was so marked as to result in fibrosis. An interesting finding was that one of the patients (not fibrosing) had polycythemia vera before the onset of leukemia and another (fibrosing) had possibly had mild myeloproliferation, as judged

from the somewhat high values for hemoglobin and WBC. One might consider the possibility of some relationship with the myeloproliferative group of diseases in these cases. It might be of interest to note that mitogen stimulated lymphocytes have been found to produce colony-stimulating factor in vitro (53).

The findings were interpreted as indicating that groups 1 and 2 were different types of the same disease. According to what is said later (see chapter 8) the mature lymphocytes are probably derived from the immature cells. It is, then, not unreasonable to assume that the cytology of the tissues is more immature than the blood picture. In those cases where a higher percentage of immature cells are released into the blood, the hematologic picture will be that of prolymphocytic leukemia. It is not possible to decide from these findings whether the picture of LLD-2 in the lymph nodes can occur also in such cases where the blood cytology is mature. However, in the light of the aleukemic case it appears probable. This type of lymphatic leukemia thus appears to occur in an aleukemic form, possibly because the immature cells in the tissue have a stronger tendency to adhere to one another than mature lymphocytes.

GROUP 1-3.

Four cases were referred to this group.

109/67 was a woman who had died at 83 years of age, after a course of 133 months. At diagnosis she had enlargement of the cervical lymph nodes, but the liver and spleen were not palpable. WBC 124,000 with 95 % lymphocytes. Hb 12.0 gram/100 ml, platelet count normal. Immunoglobulin values low. Coombs' test positive. No signs of hemolysis. Treated with corticosteroids and did well for several years. Differential count showed successive increase in percentage of "blasts", which reached a maximum of 20 %. Immunoglobulin values increased successively to abnormally high values and reached 1.8 gram/100 ml, at which level they persisted for a year or so and afterwards fell shortly before the patient died. WBC varied markedly, with a maximum of about 250,000. The patient died after operation for carcinoma of the colon. Necropsy showed sparse, diffuse lymphocyte infiltrates without enlargement of any organs. The bone marrow picture was of small-cell type with many irregular nuclei and many "diplococcoid" nuclei resembling the picture in 799/73 in group 3 with irregular chromatin structure but few with distinct nucleoli (fig. 82).

Clinically, the case resembled most CLL, but with an increasing percentage of atypical and immature cells in the blood.

437/67. The patient was 63 years old at death. Two hundred and forty-six months before death he had fallen ill with abdominal pain, for which no explanation was found and which soon disappeared. At that time he had 29,000 WBC with 78 % lymphocytes. Mildly enlarged tonsils, otherwise no enlargement of any organ. Hb 16.0 gram/100 ml, E.S.R. 1 mm/ 1 hr. The patient felt well for almost 20 years and belittled his disease, but was followed up every fourth year and the WBC increased successively to reach a maximum of 174,000. Hb, platelets and E.S.R. remained normal. Five years before death the patient was examined for the first time with electrophoresis which showed a low immunoglobulin value, 0.39 gram/100 ml, and an M-component of type IgGK of 0.30 gram/100 ml. Five later electrophoretic examinations, the last just before death, showed similar values. Bone marrow exa-

mination 4 years before death showed dense infiltration with cells of varying size and many with irregular nuclei and chromatin structure but few with distinct nucleoli (fig. 73). Many cells with deep nuclear clefts. The blood picture was similar (fig. 72).

Seven months before death a tumour developed in the mesopharynx which at biopsy was found to be HL (figs. 74, 75). Radiotherapy was without effect and the patient died from extension of the tumour into the brain. WBC terminally fell during radiotherapy and corticosteroid therapy. Necropsy showed generalised HL. The spleen contained IF. The patient had thus had almost asymptomatic leukemia for 20 years and later developed HL, from which he died within 7 months. The condition resembled most CLL.

1029/71 was a woman, 63 years old at death, who after a traffic accident was found to have splenomegaly with no palpable lymph nodes. WBC 9,300 with 84 % lymphocytes. Hb and platelets somewhat low. Immunoglobulins normal. Bone marrow aspirate showed fairly dense infiltrates of a type resembling that in group 3 with small cells with an irregular nucleus and chromatin structure and immature ++. But the blood contained mainly normal forms.

The patient felt well and did not seek advice for the following 6 years. She afterwards returned with gastrointestinal bleeding. WBC was then 66,000 with 90 % lymphocytes. The spleen had grown considerably, while the lymph nodes were still of normal size. Moderate thrombocytopenia. The source of bleeding was not found. Irradiation of the spleen was followed by severe leukopenia and thrombocytopenia, and one month later the patient died from diffuse bleeding from the gastric mucosa.

During her last spell in hospital examination of a new bone marrow aspirate revealed atypical cells but in a low percentage relative to that of apparently normal lymphocytes. The blood picture showed only occasional atypical cells. The WBC on that occasion was about 20,000.

Necropsy showed insignificant lymph node changes and focal bone marrow infiltrates as well as insignificant infiltration in the liver. The spleen weighed 2,300 g. but this was due to a thrombus in the portal vein, and it contained no residual infiltrate.

Clinically and anatomically this case would best fit in with LLD-3 with the changes localised mainly to the spleen, but especially on the last occasion, the cytologic picture of the bone marrow was so mature and so little atypical that the case was assigned to the uncertain group. The blood picture was throughout mainly of type 1 and it is at any rate uncertain to classify a case simply on the basis of the blood picture, which can be dominated by morphologically almost normal forms also in bone marrow of morphologic type 3.

913/72 was a man who died at 81 years after having fallen ill with pneumonia 49 months earlier. No palpable enlargement of any organs. WBC 15,800 with 72 % lymphocytes. Mild anemia.

Immunoglobulin levels were high with a small M-component, IgG 0.39 gram/100 ml. The bone marrow showed 90 % lymphocytes with roughly equal distribution between lymphocytes of normal appearance and cells with uneven nuclei with small

nucleoli and irregular chromatin structure (fig. 81). The patient was in a good condition, but since the WBC showed a tendency to increase, he was treated with corticosteroids, after which the WBC fell to its original level. The immunoglobulin values fell, but not to subnormal level. The concentration of the M-component rose somewhat. The patient died from myocardial infarction. Necropsy showed insignificant organ lesions, but small IF in some of the lymph nodes. The case resembled most CLL.

GROUP 4.

The picture of the bone marrow was characteristic of Waldenström's macroglobulinemia in 5 cases (225/61, 204/69, 891/69, 820/70 and V. 251/73). Such a diagnosis required a finding of mainly small-cell lymphocytic type with preponderance of lymphocytes with a mature nucleus. The characteristics of the cytoplasm were regarded as not being essential. Neither were such "lymphoid reticulum cells" with almost total lack of demonstrable cytoplasm as described by e.g. Rohr (59), though they were often seen. Further, the diagnosis required a distinct plasma cell component and transitional cells between the lymphocytic and plasmocytic population and further an increase in the mast cells. The numerical increase in the mast cells is difficult to estimate because they tend to be destroyed in association with the preparation of the smear, but in all the cases in this group the mast cells were so numerous that they were obviously increased. An increase in mast cells was common also in group 3 and did not appear to be of any differential diagnostic value. Another characteristic, which was not seen in all cases, probably due to the less satisfactory technical quality of the negative smears, was groups of cells made up of reticulum cells, lymphocytes, plasma cells and often mast cells (figs. 83, 84). One cannot make a diagnosis simply on the basis of such groups because they occur also in other conditions, e.g. often in LLD-3. Often, but not always, the plasma cells and lymphocytes exhibited intranuclear vacuoles (fig. 85) and sometimes markedly angular plasma cells were seen (fig. 83). It would appear that such cells had become detached when being smeared on the slides and had dried in this shape before they had had time to become round. In the tissue these cells have a tendency to be angular, which is the most space-saving shape with maximal surface contact. Cells with such a distinctly angular cytoplasm were seen in 3 cases, all with distinct groups of the type described. In the other cases the smears were poor in cells.

Monocytes and blast-like cells of somewhat dubious classification were also often increased, as was stainable iron. Monocytosis was often seen in the peripheral blood. In 1 case monocytes repeatedly constituted 15 to 20 % of the cells in the blood.

In all 5 cases the clinical diagnosis was Waldenström's macroglobulinemia. This also was the case in a further 2 patients in the Malmö-series. In one of them the bone marrow had not been examined. In one (99/62) the bone marrow picture was of another type, which assigned it to the unclassifiable group. All these cases are discussed together in chapter 7.

None of the cases with a clinical diagnosis of macroglobulinemia had a bone marrow picture of the type seen in group 3, but LLD-3 and macroglobulinemia had certain similarities in smears, particularly the tendency to grouping of cells and increase in the number of mast cells.

GROUP 5.

99/62. This case had a cytological picture with some similarities to myeloma. Clinically the case was macroglobulinemia and is described in chapter 7.

GROUP 3.

The diagnoses based on biopsy or necropsy specimens were as follows:

LLD-3	7 cases
LLD-4	5 cases
LLN	2 cases
undifferentiated lymphoma	3 cases.

Twelve of these cases have been dealt with in chapter 4.

Case 799/73, from which no lymph node biopsy had been obtained, was interesting as the patient had a morphologic marker cell. This case is described below.

The patient was a 71 year old man who had sought advice because of fatigue. He had considerable enlargement of the spleen and mild generalised lymph node enlargement. Hb 12.5 gram/100 ml, platelets 32,000/ μ l. Polyclonal increase of IgA, normal IgG and decreased IgM. The WBC was 8,800 with 24 % lymphocytes, which were small with sparse cytoplasm and of normal nuclear structure. 15 % of them had 2 nuclei or 1 deeply indented nucleus, each lobe of which mirrored the other (fig. 67). The laboratory assistant had not noticed the abnormality. The bone marrow smear showed 40 % lymphoid cells. Of these, more than 50 % had 2 nuclei and were of the same type as in the blood (fig. 66). A few of them had a blast-like nucleus and occasionally visible nucleoli in both nuclear lobes. Other bone marrow cells, also reticulum cells and plasma cells, were normal. Owing to the fairly small increase in lymphocytes and the preponderantly mature appearance of them, the examiner had regarded the bone marrow aspirate as normal. The patient received no treatment and died in a few days.

Necropsy showed generalised LLN. In many sites incipient transformation to HL was seen (fig. 68). The bone marrow showed diffuse infiltration with the small "diplococoid" cells. A large percentage of the lymphoma cells in all infiltrates had a bi-lobed nucleus or 2 nuclei. This applied both to the actual nodules, where the cells were larger and immature (fig. 69), and the internodular tissue, where mature forms of lymphocytes corresponding to those in the blood were predominant (fig. 70). Many HL-cells had distinct 2-lobed or double nuclei and some closely resembled Reed-Sternberg-cells (fig. 71). This can, however, be seen in all HL-cases and its significance can be questioned.

Two years before death the patient had been admitted for anemia investigation. No palpable organ enlargement was found then. The bone marrow and the blood picture was normal with a normal percentage of lymphocytes, and no "diplococoid" cells were found despite a careful review of these smears.

The cells in the blood thus were of normal appearance apart from the abnormality of nuclear shape. The actual lymphoma nodules and a small part of the bone marrow cells were immature. The internodular tissue in the lymphomas was of mature type, but with a considerable percentage of "diplococoid" cells. The binucleate lymphoma cells in the nodules and the mature internodular cells and those in the blood were probably genetically related. The findings suggest that the internodular

tissue in the nodular lymphomas also consist of abnormal cells, though often morphologically without immaturity or atypia. One might also conclude that a moderate number of cells may be shed into the blood in a patient with normal WBC, and that they may have a normal appearance though they belong to the tumour population. At least the cytologic abnormality, if any, may be very subtle.

Case 413/61 will also be described, as it was the only one in group 3, where a diagnosis of macroglobulinemia was considered. The patient, however, had a monoclonal IgG-component. Six years before being admitted to hospital the patient had had obscure abdominal pain and the blood values at that time had been normal, as had the E.S.R. The patient now was admitted for investigation of anemia. Hb 5.6 gram/100 ml. Overt hemolysis. Coombs' test was positive. WBC 6,500 with 75 % lymphocytes. Platelet count 114,000/ μ l. Electrophoresis showed background immunoglobulin of 0.33 gram/100 ml and an M-component of 1.1 gram/100 ml of type IgGK (classification controlled and correct). The spleen was slightly enlarged, no lymph nodes were palpable. The bone marrow aspirate was poorly cellular with a predominance of lymphocytic cells, often in clusters. They varied in size and shape and most had a fine chromatin net but few demonstrated visible nucleoli (fig. 105). Abundant mast cells and numerous plasma cells with a normal morphology. Large amounts of hemosiderin pigment. The picture thus resembled macroglobulinemia, but no transitional forms between plasma cells and lymphocytes were seen and the lymphocytes were subtly different from those in a classical case of macroglobulinemia.

The patient was treated with corticosteroids with a moderate effect on hyperhemolysis but blood transfusions were necessary and the platelet values successively decreased. The WBC rose slowly with an increasing percentage of "atypical" lymphocytes. Maximum 10,800 with 92 % lymphocytes.

Splenectomy was done after 19 months without any notable effect. The spleen weighed 480 g and had almost empty malpighian corpuscles and the red pulp showed a sparse lymphocytic infiltrate. After splenectomy the M-component divided into 2, both of IgG-type. They had concentrations of 1.13 and 1.56 gram/100 ml. The patient died 5 months after the splenectomy, 2 years after diagnosis, of thrombocytopenic haemorrhages.

The picture of the bone marrow in sections obtained at necropsy was difficult to distinguish from that in macroglobulinemia: diffuse but fairly sparse infiltration of lymphocytic cells, abundant plasma cells and mast cells, diffusely scattered in the lymphocytic cellular flora. All lymph nodes were atrophic and no lesions whatsoever were found in them. The liver showed portal fibrosis with lymphocytic infiltrates of considerable dimensions.

From a morphologic point of view, the diagnosis of macroglobulinemia was considered in this case. However, no plasmacytoid cells with morphology intermediate between plasma cells and lymphocytes were seen. Also, the lymphocytic cells were more atypical and had less coarse nuclear structure than what is commonly seen in macroglobulinemia. Because of this, the case was referred to group 3. Probably it should be classified as LLD-3, but the absence of lymph node lesions makes it impossible to place in the lymph node classification scheme. It is evident that tumour

of the lymph nodes need not be an obligatory component of such processes. (This case is not included in the necropsy series of LLD-3).

Three of the cases in this bone marrow group were judged as undifferentiated lymphoma in the lymph nodes. These cases will not be further dealt with in the necropsy material but they are described below.

Case 878/64 was examined 1 month before death. She then had a leukemia with WBC 282,000 with a preponderance of lymphocytes, some atypical. The majority of cells were quite mature, however, and the blood picture was certainly of lymphocytic type (fig. 111). The bone marrow, however, was dominated by blastic cells without evident lymphocytic features (fig. 110). This patient had had a lymphoma in the anterior mediastinum for 50 months. A biopsy of the lesion had been obtained at the time of diagnosis and had been interpreted as "lymphosarcoma". Review demonstrated undifferentiated lymphoma with a monomorphous picture of small, blastic cells. The necropsy specimens showed the same kind of infiltration.

The case illustrates that the leukemia of undifferentiated lymphoma may be quite lymphocytic in type. As cells from the blood contaminate the bone marrow smear there will be a mixture of blasts and lymphocytic cells, giving a confusing picture.

In case 841/73 the bone marrow picture was similar. The patient survived only some days after diagnosis and had occasional atypical lymphocytes in the blood.

Case 633/68 had a bone marrow picture, which was dominated by small, lymphocytic cells with rather coarse nuclear structure. Also larger, blast-like cells with sparse cytoplasm were present, however (fig. 109). There was no distinct division into generations but a continuous anisokaryosis. WBC 3,500 with 59 % "lymphocytes" and 15 % "blasts". The patient died after 2 months without therapy. The spleen, liver and kidneys showed extensive infiltrates of quite undifferentiated, blastic cells. The nodes were moderately enlarged and were dominated by similar cells. In many places there was a pattern suspected of nodularity. Possibly the case represents a transitional form between nodular lymphoma and undifferentiated lymphoma.

DISCUSSION OF BONE MARROW SMEARS.

The bone marrow picture described as group 1, corresponding to the lymph node picture of LLD-1, is always correlated with the hematologic picture of CLL. In practice, these pictures of the marrow and lymph nodes are never seen in aleukemic disease. It is possible that an occasional case of incipient CLL may show these pictures of the tissue without a leukemic blood picture, but in this phase the disease is rarely investigated.

The picture of the lymph node in LLD-2 is presumably always associated with the hematological picture of prolymphocytic leukemia. This sometimes, but not always, applies to the bone marrow picture of group 2.

Groups 1 and 2 are characterised by 2 easily distinguishable types of cells, the mature lymphocytes and the prolymphocytes. The cytologic picture in group 3 is more polymorphous. Separate generations are not readily distinguished, but there is a continuous dyskaryosis and anisokaryosis. Generally, the technical quality of the smears is poorer than in LLD-1 or LLD-2. This may in part be the explanation of the difficulty of separating LLD-3 and LLD-4 and undifferentiated lymphoma. Generally, cellular and good smears are obtained only if the patients are leukemic. It may

appear strange that it is difficult to distinguish between LLD-3 and LLD-4 or undifferentiated lymphoma. Clinically, these conditions are very different. With highly cellular and technically perfect smears it should be possible to estimate the percentage of pure blast cells and if this percentage is high the case probably belongs to the undifferentiated group. It should, however, be pointed out that also in this group a large percentage of the bone marrow cells may be small and seemingly mature lymphocytes, even if they are atypical. The blood picture in leukemic cases of undifferentiated lymphoma is not necessarily blastic. In some cases of undifferentiated lymphoma there may be a slight tendency to nodularity in the nodes and it may be a sign of a relation between these diseases. There is a possibility that the nodular lymphomas may progress to undifferentiated forms, but this needs further study in larger materials. If this is so, it could be the explanation of the difficulties in distinguishing undifferentiated lymphoma and LLN or LLD-4 from the bone marrow pictures.

LLD-3 is astonishingly polymorphous in the bone marrow and here it is easier to confuse the picture with LLD-4 or undifferentiated lymphoma, while it is easier to confuse LLD-3 and LLD-1 in the lymph node histologic picture. Generally, there is a higher percentage of cells with condensed chromatin in LLD-3 and a lower percentage of cells with very immature nuclei than in undifferentiated lymphoma. Also, the cases generally have a high percentage of plasma cells in the marrow, but they appear morphologically normal and cannot be used as a reliable criterion for the assignment of a case to this group. The prolymphocytes are not a characteristic feature of the bone marrow picture of LLD-3, though occasional such cells can generally be found.

The most characteristic feature of the bone marrow cells in LLD-4 and LLN is the highly wrinkled or notched nuclear shape. In some cases, this feature may not be very pronounced, however, and it did not appear meaningful to try to demonstrate the differences between LLD-3 and LLD-4-LLN objectively. An experienced examiner will probably be able to guess to which group the case belongs, but it is nevertheless recommended to obtain a biopsy specimen of the lymph nodes in cases with atypical bone marrow cytology.

It is occasionally uncertain whether a case should be assigned to group 1 or group 3. Clinically, they may resemble LLD-1 or LLD-3. Biopsy specimens of the lymph nodes were missing in the doubtful cases in this series, for which reason it is not possible to know whether such a specimen would have helped to classify the cases. In 2 cases, however, IF were seen in necropsy specimens and these cases should therefore presumably be referred to LLD-1. Such cases difficult to classify suggest that there are close connections between the various lymphoma groups. It might be questioned whether it is of any practical value to distinguish between LLD-1 and LLD-3 in leukemic cases. Probably the prognosis is worse in LLD-3 once the leukemia has appeared, however. The doubtful cases are relatively few compared to the whole material.

Schwartz et al. (63) used the term acute and chronic lymphosarcoma cell leukemia. Acute lymphosarcoma cell leukemia probably corresponds to leukemic cases of LLD-4 or LLN, and possibly also cases of undifferentiated lymphoma with a

lymphocytic blood picture. Chronic lymphosarcoma cell leukemia probably corresponds to LLD-3 in leukemic phase, and possibly also some cases of LLD-4 or LLN. If the term lymphosarcoma is omitted from the nomenclature, lymphosarcoma cell leukemia should not be used either. As a name, I suggest lymphoma cell leukemia with specification of the type of lymphoma in question in the nomenclature system used. For a full classification of a given case, lymph node biopsy will thus generally be necessary.

Chapter 6

NECROPSY MATERIAL

Sixty patients in the Malmö series were not examined with either biopsy of a lymph node or bone marrow aspiration. These cases are therefore generally classified only on the basis of necropsy findings. Some cases, however, were classified on biopsy material from other organs than nodes or bone marrow.

Nodular lymphocytic lymphomas can readily be diagnosed in necropsy specimens. Small-cell processes, such as LLD-1, LLD-3 and small-cell LLD-4 may be difficult to distinguish because of autolysis and cell swelling or shrinkage. Prolymphocytes are often difficult to discern because of the clumping of chromatin, which may take place post mortem. This is probably the chief reason why IF are sometimes difficult to detect in necropsy specimens. Yet, there are generally parts of the infiltrates that are sufficiently preserved to allow classification, if many tissue blocks are examined.

The cases were classified as follows:

LLD-1	45
LLD-2	2
LLD-1 (+2)	1
LLD-3	2
LLD-4	2
Status after LLD-4	1
LLN + HL	1
LLN + D	5

This classification calls for commentation.

The case "status after LLD-4" had a tumour of the tonsils verified by biopsy 13 months before death. It was of the small-cell type with very few blasts. No new manifestations appeared after radiotherapy. The patient died from arteriosclerotic disease, and at necropsy no signs of tumour were seen. The case showed that processes of this type can occur as solitary lesions.

Of the cases LLN + D the diagnosis in 2 was made at necropsy of patients in whom the disease had not been suspected during life. Both were aleukemic. Two others, also aleukemic, had been clinically misinterpreted as other malignant tumours (pancreatic carcinoma and mesothelioma of the pleura). In none of these 4 cases was the bone marrow involved. The 5th patient had a lymphoma diagnosed intra vitam. Four months before death the epipharynx was found to harbour a tumour of LLD-4-type. One week before death "blasts" (67 %) appeared in the blood when the WBC was 9,900. At necropsy LLN + D was found in many organs including the bone marrow, as well as extra-lymphatic tumours.

The case LLN + HL (737/69) was interesting. A 65-year old man, who died from myocardial infarction. At necropsy a walnut-sized submucosal gastric tumour was

found, which was LLN without signs of HL (fig. 107). Further, a somewhat smaller tumour in the spleen. It was also microscopically nodular and built up of central HL-foci surrounded by brims of lymphocytic lymphoma (fig. 108). The appearance gave the impression of HL starting in LLN. The spleen was otherwise normal as were all other organs. This tumour had probably developed as a HL in the spleen if the patient had survived longer and the tumour process would probably have spread like HL. Such small lesions in internal organs are rarely, if ever, discovered *intra vitam*. The findings suggest the possibility that tumours diagnosed as HL may have had a concealed pre-stage as LL.

The extent of lesions in the cases of LLD-4 and LLD-3 is given in table 11.

LLD-4	Bone marrow	Spleen	Liver	Nodes
1042/70	-	-	+	RP
706/71	Focal	-	+	RP
LLD-3				
690/60	Focal	+	+	RP
290/70	Focal	+	+	All LL or HL see text

Table 11. Cases of LLD-3 and LLD-4 in necropsy series. RP = retroperitoneal nodes.

Case 290/70 (see table 11) had the first symptoms from HL in nasal polyps. LL was not diagnosed before necropsy. The case is reported later.

Two cases were judged as LLD-2 (1305/64 and 929/61).

1305/64 was a woman, aged 78 at death. She lived for 45 months after the diagnosis. The WBC was high, 200,000-300,000, with a varying percentage of "lymphoblasts". The liver and spleen were markedly enlarged, as were the lymph nodes. The patient was troubled by back pain. At necropsy alternating osteolytic and osteosclerotic changes were found in the vertebral bodies and also fibrous areas with lymphocyte infiltration. Massively hyperplastic myelopoiesis and increased megakaryocytes. In the lymph nodes small necroses were seen with histiocytic infiltration and also calcification. The findings thus resembled those in other cases of LLD-2 described earlier.

929/61 was an 89-year old man who was aleukemic. He died from gangrene of the leg. The diagnosis was not made before necropsy. The bone marrow showed focal infiltration. All nodes were engaged with lesions of type LLD-2. Here, then, was another aleukemic case with this picture of the lymph nodes.

In one patient the disease had been diagnosed intra vitam as CLL with "a blastic crisis".

This is the only patient in the series who had shown a blastic transformation in the sense of a fairly abrupt change in the clinical condition and cytologic picture of the blood. The patient was a 63-year old man who had fallen ill with pneumonia. WBC 23,000 with 75 % lymphocytes. No enlargement of internal organs. Low immunoglobulin values. After treatment of pneumonia he first improved, but one month before death his general condition suddenly deteriorated. The WBC rose abruptly and the differential count showed 50 % "blasts" (slide not available) and 50 % neutrophil leukocytes. The patient died 3 months after diagnosis and necropsy showed focal bone marrow infiltrates. Most lymph nodes exhibited a picture assigning the case to LLD-1, though IF were not easily recognized. The mediastinal nodes showed immature cells diffusely mixed with small lymphocytes without distinguishable IF, thus a picture resembling LLD-2 (fig. 106). The immature cells were negative in chloracetate-esterase reaction and there were no other signs of a possible myeloblastic leukemia. This case thus resembled a true "blastic crisis" of a CLL. Nothing further can be concluded from this single case about this type of the course of the disease.

Of the 45 cases judged as LLD-1, there were adequate clinical examinations in 36. They were all leukemic at the time of diagnosis. Twenty-three of them had died from lymphoma disease, 13 from some other condition. The average age at death of the 23 was 76 years, thus roughly the same as in the patients from whom biopsy specimens had been obtained.

The immunoglobulin values in the CLL-cases are summarised in table 14. One case had initially high diffuse values, which afterwards fell to low levels and afterwards rose again. This increase was accompanied by the appearance of Bence Jones proteinuria. In addition, 3 monoclonal immunoglobulin components were found, including 2 in the form of kappa-chains in the urine, the 3rd as a small IgMK in the plasma. Coombs' test was positive in 2 of 15 cases examined.

The necropsy findings in these 36 cases showed generalised lesions in all except 5 in which one of the lymph node sites was without diagnostic lesions. Changes in the bone marrow, liver and spleen were found in all. In none of the cases were any extra-lymphatic lymphoid tumours found. One had HL, one Hodgkin's disease. These cases are described later.

Two had myocardial amyloidosis of the "senile" type (75 and 87 years old).

A further 9 cases were apparently CLL. The clinical examinations were incomplete. Five had increased WBC without any differential count, in 3 no blood values were noted. All the patients had generalised lesions without extra-lymphatic tumours. One of the patients had died from generalised zoster with adrenal necrosis without any known preceding ill health.

One patient (902/71), a 91-year old man, who had died from pneumonia, had 9,500 WBC. No differential count. Necropsy had shown moderately wide-spread, focal bone marrow infiltrates and slightly enlarged lymph nodes retroperitoneally. They showed a picture that would fit in well with LLD-1 and suspect IF. Other lymph nodes were not enlarged and showed only suspect pathologic changes. The

liver and spleen appeared normal. This case was probably an instance of "aleukemic CLL", in which the patient had died so early in the course of the disease that diagnostic general changes had not had time to develop. However, the bone marrow and at least one lymph node site were involved. It is not known whether the patient had absolute lymphocytosis but the WBC was not increased with certainty.

For practical reasons LLD-1 of the biopsy and necropsy series and bone marrow group 1 will henceforward be referred to as LLD-1 without specification.

It is evident that there are differences in the prevalence of the lymphoma groups in a series of lymph node biopsy specimens and a necropsy material. The chief reason for the lower frequency of LLD-1 in the material of lymph node biopsies is, of course, that biopsies are not often obtained in clinically characteristic cases of CLL. Cases of prolymphocytic leukemia are probably more prone to be biopsied because of the alarming blood picture. As has been pointed out earlier, it may be difficult to distinguish LLD-1 from LLD-2 in necropsy specimens, because of postmortal changes. Generally, IF can be detected in some tissues at necropsy of LLD-1, but if autolysis is pronounced, it may be rather difficult. In such cases with poor preservation of the cytological picture it is not recommended to try to distinguish LLD-1 from LLD-2 in necropsy specimens. Thus, an occasional case in this series may be incorrectly classified, though the 2 necropsy cases judged as LLD-2 were well preserved.

Some uncertainty also may pertain to the classification LLD-1 or LLD-3, in cases where IF are difficult to detect for technical reasons. The plasma cells, which are easily found in LLD-3 but very sparsely in LLD-1, are generally easy to find also in necropsy specimens, however, and it is felt that the separation of these two processes can be made in necropsy specimens with reasonable accuracy. Why, then, is the picture of LLD-3 so rarely met with in necropsy specimens? I think that this is best explained by the assumption that a high percentage of cases with LLD-3 transform to HL before death. The early phase of LLD-3 is probably often an asymptomatic disease and in many cases of HL diagnosed at necropsy or biopsy, LLD-3 may very well have existed for a long time without affecting the health of the patient.

As has been pointed out in chapter 4, the demarcation between LLN and mixed histiocytic-lymphocytic nodular lymphoma is somewhat arbitrary for which reason comparison of the frequency of nodular lymphomas with other statistics is uninteresting. The group of nodular lymphomas, as a whole, is the largest in the nodal non-Hodgkin's lymphoma series of the institute at present. In the material of cases diagnosed at necropsy the nodular lymphomas are not very frequent. This also may be taken as a sign of a transformation to HL before death in a large number of such cases. It is also my impression that undifferentiated lymphomas are diagnosed much more frequently in necropsy material than in biopsy material. This may possibly be a sign of other types of lymphoma developing an undifferentiated cytologic picture before death. The nodular lymphomas and the undifferentiated lymphomas, however, were not studied as groups in this material and this point will not be further dwelt upon.

DIAGNOSIS	NUMBER ALL (M/F)	DIED OF LYMPHOMA ALL (M/F)	MEAN AGE AT DEATH OF THOSE WHO DIED OF		MEAN SURVIVAL OF THOSE WHO DIED OF LYMPHOMA, MONTHS ALL RANGE (M/F)
			LYMPHOMA, ALL RANGE (M/F)	YEARS ALL RANGE (M/F)	
LLD-1	94 (62/32)	57 (42/15)	74	50-88 (74/75)	45 0-180 (44/47)
LLD-2/GROUP 2	12 (7/5)	10 (6/4)	74	53-92 (72/76)	36 0-148 (37/35)
LLD-3	9 (5/4)	6 (3/3)	67	58-84	52 7-137
LLD-4	15 (11/4)	13 (9/4)	65	35-84	44 7-126
LLN	13 (7/6)	11 (5/6)	69	52-95	24 0-70

Table 12. Total material. Cases of macroglobulinemia and doubtful classification not included.

Certain data on the entire necropsy material are given in tables 12 and 13. Broadly speaking, the figures agree with the smaller biopsy material. All the groups showed a shorter average survival because they included the cases that were diagnosed at necropsy and those in which the patient did not seek advice until the disease was advanced and who died soon after the diagnosis. Most of them probably had had symptoms for some time, but it was often not possible to say anything certain from the preliminary notes made on admission of the patients and no attempt will be made to analyse the figures. The smaller groups are not sufficient for statistical significance and the survival figure for LLN, for example, is misleading, as in 3 of the patients who died of lymphoma the disease was not diagnosed as such before necropsy, and nothing is known about the previous clinical history of the patients. If the figures of age at death of those who died of lymphoma are judged in relation to the roughly estimated survival figures given in chapter 4, it seems probable that LLD-3 generally starts somewhat earlier than LLD-1 or -2. It also appears probable that LLD-4 and LLN may occur in younger patients than LLD-1, -2 or -3. But they are also seen in extremely old people.

	Range	Percentage > 60 years
LLD-1	48-92	92
LLD-2/Group 2	52-88	92
LLD-3	53-83	56
LLD-4	33-86	60
LLN	47-95	69

Table 13. Age at the time of the diagnosis in total necropsy series.

The longest survival time in the entire material was that of a man in bone marrow group 1-3, who fell ill at 43 years and lived for a further 246 months.

The age at the time of diagnosis is given in table 13. The youngest in the CLL group was a woman, 48 years. Three in this group lived for more than 10 years after the diagnosis, 122, 160 and 180 months.

In all the groups the majority of the patients were males. The sex distribution cannot be judged with anything like certainty from the figures in the small groups. LLD-1 is probably twice as common in men as in women. LLD-1 is primarily a disease of old people and from a statistical point of view shortens the expectancy of life but little.

In 34 of 94 in the LLD-1 series clearly malignant tumours of non-lymphatic type (basal cell epithelioma and latent prostatic carcinoma and myeloma included) were

diagnosed during the course of the disease or at necropsy. Of these, 7 had more than one type of tumour histologically. In addition, 2 had hypophyseal adenoma and 4 meningoma.

If we add LLD-1, bone marrow group 1-3 and LLD-2/bone marrow group 2, it will mean 110 cases. These groups probably approximately correspond to cases generally included in series of CLL in the literature. 41 of 110 had clearly malignant tumours (including the above) of non-lymphatic type, *i.e.*, 37 %. Owing to the small figures, it is meaningless to count the various types of tumours separately. The overall frequency does not exceed that of the material of the department of pathology as a whole (in a large material from approximately the same period 38 % of necropsied cases had carcinomas (7)). Space will not permit analysis of the figures. In LLD-3 the only non-lymphatic malignant lesion was Bowen's disease in case 855/67.

In the LLD-1 series, 15 had zoster on some occasion during the course (16 %). Zoster also was seen in one patient in group 2, one in group 1-3 and one in LLD-3. One of the macroglobulinemia patients (chapter 8) also had zoster. In LLD-4 and LLN, altogether 28 cases, zoster had been noted in 3 patients, all of whom had low immunoglobulins.

In LLD-1 there was one case of progressive multifocal leukoencephalopathy, one of necrotising cytomegalic virus infection in the adrenals, one with large amounts of recurrent mollusca contagiosa, one pneumocystis carinii pneumonia, one toxoplasma myocarditis, and one listeria meningoencephalitis. No such infections were found in the other groups.

Pulmonary mycosis was seen in one case of LLD-1, one case of bone marrow group 2 and one case of LLD-3. Active tuberculosis of the lungs or other organs was found in 6 cases of LLD-1, including 2 with fatal miliary tuberculosis. Tuberculosis was also found in one patient in bone marrow group 2 and one in LLD-4 (high immunoglobulins). One of the LLN-patients had renal tuberculosis of long standing, the only case in the series where the tuberculosis was diagnosed *intra vitam*. Tuberculosis was at least as common during the latter part of the period as in the former part and is obviously still a serious risk in patients with lymphoma and lymphatic leukemia.

The immunoglobulin values are given in table 14.

In LLD-1 there was one patient with myeloma (not included in the table) of IgG-type. In addition to this case 11 monoclonal immunoglobulin components, all probably of IgM-type, were found in all together 77 patients who had been examined some time in the course of the disease.

In bone marrow group 2, one monoclonal component (IgM) was found.

In group 1-3 (4 examined) 2 had low immunoglobulin values early, 1 normal, 1 high. Two monoclonal components were found, both IgGK.

In LLD-3 4 patients had monoclonal immunoglobulin components on some occasion. Two of them were found only in the urine as light chains, one kappa and one lambda. In one case it was a question of an IgG in the serum and in one case an IgM in the serum.

One of the cases of LLD-4 had a small component in the serum electrophoresis in β -2, not examined further.

One of the patients in LLN had an IgGL monoclonal component in the serum electrophoresis.

DIAGNOSIS	NUMBER OF CASES EXAMINED	LOW	NORMAL	HIGH
LLD-1				
EARLY	74	44	21	9
LATE	47	38	5	4
LLD-2/GROUP 2				
EARLY	8	4	2	2
LATE	6	5	0	1
LLD-3				
EARLY	5			5
LATE	7	1	2	4
LLD-4				
EARLY	11	5	4	2
LATE	11	6	2	3
LLN				
EARLY	5	1	3	1
LATE	7	4	2	1

Table 14. Immunoglobulin findings in total material.

Chapter 7

MACROGLOBULINEMIA SERIES

This chapter concerns all cases with a clinical diagnosis of Waldenström's macroglobulinemia. In 5 of the Malmö-cases the bone marrow was examined and the findings were of the "classical" type and have been described under group 4 in the chapter on the bone marrow material. A further 2 cases in the Malmö-series had this clinical diagnosis. In one (V. 434/71) there was no bone marrow examination, in one (99/62) the picture of the bone marrow was of different type, described below. Two cases not belonging to the Malmö-series are included in this chapter. They also had Waldenström's macroglobulinemia diagnosed clinically.

All these 9 cases are the subject of this chapter. Three had peculiar features; the remaining 6 will be treated first. They had a picture of the bone marrow smears of classical type. Four of the patients were women, 2 were men. The age at death ranged from 49 to 92 years and the survival time from the diagnosis from 49 to 180 months (average 92 months). The youngest patient at the time of onset (33 years) and the one who survived longest (about 15 years) was a woman (777/68), who eventually died from HL. The M-components were of type IgM in all. Light chains were typed in 3. Two were kappa and one lambda. The highest concentration varied from 2.3 to 9.0 gram/100 ml. Case number V. 251/73 had 2 M-components, IgMK with maximal concentration of 2.3 gram/100 ml and IgGK with a maximum concentration of 1.5 gram/100 ml. The patient was thought to have macroglobulinemia + myeloma, but the skeleton was normal roentgenographically and the morphologic picture was that of macroglobulinemia.

At the time of the diagnosis one of the patients had a normal hemoglobin concentration, one had severe hemolytic anemia, the others moderate non-characteristic anemia. One had thrombocytopenia. The patients sought advice for various reasons: one because of zoster, one because of nose-bleeding, one because of joint pain, one because of tingling of the fingers and one because of fatigue. One was discovered incidentally at check examination of the E.S.R. at the department of geriatrics.

At the time of diagnosis none of the patients had palpable enlargement of lymph nodes, liver or spleen. Only in 777/68 was such enlargement discovered in the course of the disease (due to HL). None of these patients had ever had absolute lymphocytosis of the blood. All had considerable monocytosis on some occasion, 2 of them almost constantly. One patient died after 16 months from myocardial infarction. 777/68 died from HL after 180 months. 204/69 died after 100 months of influenza during an epidemic. The patient was in a good clinical condition and the M-component had been falling continuously during treatment with melfalan. The other 3 patients died mainly from old age, 80, 90 and 92 years old.

Two of the patients received no specific treatment (survival 146 and 49 months). The others were treated with cytostatics during some period and three of them also received corticosteroids.

FINDINGS AT NECROPSY.

204/69, who died from influenza, had insignificant focal lymphoplasmocytic infiltrates of doubtful diagnostic significance in the bone marrow. All the other organs were entirely free from infiltration. The mediastinal lymph nodes showed a striking immunoblastic reaction after influenza pneumonia of the same appearance as in many other, immunologically normal patients who died in that epidemic.

The other 5 patients showed bone marrow infiltration of diffuse type with the same forms of cells as in the aspirates obtained during life. Infiltration was never entirely compact, but a varying number of fat cells persisted, as did hematopoietic cells.

These patients had insignificant changes in the spleen. The weight of the spleen varied from 90 to 260 g. The changes in all of them had the character of a sparse, diffuse deposition of lymphocytes, plasma cells and intermediate forms in the red pulp, while the white splenic pulp was not expanded. Mast cells were irregular components of the extramedullary infiltrate and, especially, in the spleen, they were often difficult to detect.

The liver showed insignificant infiltration in the portal tracts in 2 patients, but without enlargement of the liver. Four of the 6 thus had no liver changes.

As pointed out above, the lymph nodes in 204/69 were of normal appearance. The remaining 5 had microscopic changes in the lymph nodes. All of the lymph nodes were involved, though the involvement of the inguinal and axillary nodes were generally of dubiously diagnostic character. In one all the lymph nodes were of normal size, in 3 slightly enlarged, in 777/68 markedly enlarged by HL (see below). The picture of the lymph nodes was characterised by infiltration of lymphocytes, plasma cells and intermediate forms in the cortex and medulla, but not so dense as to obliterate the sinuses. Often there was a diffuse division into fields with alternating small, lymphocyte-like and larger, plasma cell-like forms (fig. 87), the latter tending to be situated adjacent to the sinuses. The sinuses often contained abundant phagocytes, very often with phagocytosis of red blood cells. Deposition of iron was common within and around the sinus. Mast cells were seen along the sinuses and vessels, but were not with certainty more abundant than in reactive lymph nodes. No germinal centers were seen. The capsule and the pericapsular tissue always showed a certain infiltration somewhere, but not necessarily in each lymph node site. A remarkable feature of this disease was that the infiltration in the perinodal adipose tissue tended to accentuate the lobular architecture of the fat in a way not seen in LLD-1 or other lymphocytic lymphomas. The appearance was so characteristic as to warrant assumption of macroglobulinemia. When the infiltration became more dense, the lobular appearance became more compact, which could be misinterpreted as nodular lymphoma (fig. 89). It was not only cachectic patients with accentuated lobulation of the adipose tissue that showed this sign, but also patients in a good nutritional state. The phenomenon is presumably due to a tendency of the infiltrates to follow the lymphatic vessels and often they were dilatated, which

per se tended to accentuate the lobulation (fig. 90).

777/68 had HL in the inguinal and paraaortic lymph nodes. After a course of almost 15 years, during which she had received about 4.8 g chlorambucil, and corticosteroids (for details, see 82) she deteriorated rapidly within about half a year. At the same time she had increasing swelling of the legs. The concentration of the M-component had for 2 years been decreasing. Necropsy showed fist-sized sarcomatous lymph nodes inguinally and in the pelvis and retroperitoneum. Microscopically they showed HL (figs. 96,97). The bone marrow and other nodal sites still showed infiltration of the same type as in the bone marrow aspirates (figs. 98,99). The sarcomatous lesions also showed amyloid deposition (fig. 100), which were not seen in other organs. It might be mentioned that none of the other patients with macroglobulinemia showed amyloidosis, and neither did any of the other patients with lymphoma in the entire series (besides 2 LLD-1 with "senile" heart amyloidosis).

In no case did the lymph nodes show typical IF. However, there were always scattered immature, large cells with "vesicular" nuclei and large nucleoli (figs. 88, 91). The nucleus was generally irregular in shape, "monocytoid", and the cytoplasm abundant. These cells often were in mitosis. They were rarely found outside the nodes and spleen.

777/68 had alternating areas of small-cell type in the lymph nodes and areas with such large cells. These foci showed mitotic figures, often atypical, and gradual transition to HL (figs. 96, 97).

V. 251/73 (with 2 M-components) showed no signs of myeloma at necropsy.

The kidneys and renal pelvic fat tissue in 4 of these patients showed lymphocytic infiltration with a similarity to that of LLD-1, but the infiltration had a stronger tendency to spread along the small vessels and the collecting tubulus in the medulla and the upper part of papillae. One of the patients had a massive infiltrate in the mucosa of the renal pelvis, which was markedly thickened.

In 2 cases the lungs showed sparse infiltration peribronchially. One had marked interstitial infiltration in the myocardium. Another had an infiltrate in the pericardial fat. No extra-lymphatic tumours were found in the group.

THREE CASES WITH A CLINICAL DIAGNOSIS OF MACROGLOBULINEMIA EXHIBITED DEVIATING FEATURES. 99/62 had a short history (2-3 months) of increasing fatigue and headache. Admitted almost comatose. He had an IgM-component of 6.7 gram/100 ml. WBC 9,700 with 22 % cells judged as "atypical plasma-cell-like lymphocytes" and 8 % "atypical monocytes". Platelet count normal, Hb 13.0 gram/100 ml. The bone marrow aspirate was highly cellular but difficult to interpret because of a heavily stained protein film which covered all the structures. The nuclei were roughly twice the size of that of lymphocytes and had blast-like characteristics. They contained abundant inclusions, which stained PAS-positively, like the film (fig. 103). Many of the cells had a very narrow rim of basophilic cytoplasm, others clearly plasmacell-like features with abundant, basophilic cytoplasm but always more immature nucleus than ordinary plasma cells (figs. 101, 102). The patient had magnificent retinal changes of macroglobulinemia-type and developed renal insufficiency, which was interpreted as due to hyperviscosity. No skeletal

lesions were demonstrable in the roentgenogram. Treatment with melfalan was started, but the patient suddenly died 4 days later. The cause of death was a ruptured aneurysm of the superior mesenteric artery. At necropsy the bone marrow showed small diffuse aggregates of plasma cell-like elements with intranuclear, PAS-positive inclusions in virtually every cell (fig. 104). The nuclei were sometimes perforated by a large number of such small inclusions. No mast cells were seen. Plasma in the vessels was intensely PAS-positive. There was no arteriosclerosis of the cerebral arteries, but the brain was studded with haemorrhagic micromalaciae. In the red pulp of the spleen there were single cells resembling those in the bone marrow, but the spleen was small (90 g) and the liver was completely free from abnormal cells. The lymph nodes were of normal size, and contained sparse pathological cells in the sinuses but none in the parenchyma. Marked erythrophagocytosis in the RES.

This patient thus had a disease clinically characterised mainly by an uncommonly malignant hyperviscosity, a large M-component and a quantitatively insignificant infiltrate in the bone marrow, but morphologically different from the classical macroglobulinemia in that the picture was dominated by large cells with plasma cell-like cytoplasm, but a blast-like nucleus. The large amount of intranuclear PAS-positive inclusions in practically all cell nuclei did not resemble the classical picture of macroglobulinemia either. The larger forms of cells resembled to a certain extent the cells in LLD-2. There were abnormal cells in the circulation. The variation in the cellular picture was clearly different from myeloma. There were no osteolytic foci.

1224/70. This patient sought advice because of inguinal hernia. Examination revealed a WBC of 120,000 and a high E.S.R. and M-component. A bone marrow aspirate at another hospital (smear not available) was described as "well compatible with macroglobulinemia". The blood picture was described as "small-cell CLL". The patient was treated with prednisone and chlorambucil without any notable effect and the WBC showed a tendency to increase. She complained of fatigue and frequent bleeding of the nose and gums. Because of thrombocytopenia and anemia, a moderately enlarged spleen (19 x 11 x 6 cm) was removed after 20 months. The patient died from pneumonia after the operation.

At splenectomy also a lymph node was removed from the abdomen. It was moderately enlarged and showed a picture fitting in well with macroglobulinemia, as described in the section on clinical typical cases. No IF. Open sinuses. The diffuse chess-board-like distribution of large and small cells was clearly seen (fig. 87) and some blastic forms were found diffusely in the tissue (figs. 88, 91). The spleen showed well preserved Malpighian corpuscles and dense infiltration of cells in the red pulp. The cells were of the same type as in the lymph node. There was a pea-sized focus with quite another structure, which compressed the surrounding splenic parenchyma. The cells were large and polymorphous and there were numerous bizarre tumour cells with large nucleoli as well as mitotic figures (figs. 92, 93). This tissue was of HL-type. At necropsy all lymph nodes, which were insignificantly enlarged, showed the same picture as that of the lymph node extirpated in association with the splenectomy. The liver was completely free from infiltration in the

portal tracts, while the sinusoids contained numerous lymphocytes from the blood. (WBC terminally 470,000). The bone marrow showed dense diffuse infiltration of predominantly lymphocytes, but also plasmacytoid forms and mast cells, thus a picture compatible with the classical type (fig. 86). The kidneys showed dense infiltrates in the medulla. No HL-changes anywhere at necropsy.

What should this condition be called? Had the patient a CLL with a macroglobulin band in the electrophoretic pattern and not a macroglobulinemia in the strict sense of the term. In my opinion, the picture of the tissue deviated so much from classical CLL and resembled classical macroglobulinemia so much, that it is more correct to regard the condition as the latter disease. The picture of the lymph node was typical. Lack of tissue infiltration in the liver despite a high WBC was not compatible with CLL. The bone marrow picture was compatible with macroglobulinemia. On the other hand, the blood picture was that of CLL. The diseases are probably closely related and further differentiation might seem less meaningful. It nevertheless appears reasonable that macroglobulinemia can sometimes occur in a leukemic form. In the light of this consideration one might thus call the disease "leukemic macroglobulinemia" rather than CLL with macroglobulinemia. The HL-changes in the spleen would probably have grown and similar changes probably have developed elsewhere if the patient had lived longer.

V. 434/71 sought advice because of cough and fatigue. He dated the onset of his disease to an attack of influenza 18 months previously. Chest X-ray showed diffuse "probably inflammatory changes" and a large tumour in the lingula. Cytologic examination of the sputum showed squamous cell carcinoma, and treatment with cyclophosphamide was started, as surgery was regarded as out of the question.

The E.S.R. was 100 mm/1 hour and electrophoresis showed 3 M-components, one IgMK of 2.45 gram/100 ml and one IgGK of 2.0 gram/100 ml and a small IgAK of 0.42 gram/100 ml. The concentration of the first 2 was found to be increasing at later controls. Bence Jones proteinuria type kappa. The differential count showed neutrophilia and often monocytosis, but never lymphocytosis. The bone marrow was not examined. Treatment had no demonstrable effect on the lung changes and the patient deteriorated and died in a cachectic state after 14 months.

Necropsy showed no carcinoma of the lung; the tumour was instead built up of the same forms of cells as those forming widespread, diffuse interstitial infiltrates of the lung. These cells consisted of small lymphocytes and plasma cells and intermediate forms and "monocytoid" blasts. There was a diffuse division into fields with lymphocytes and plasma cells separately, but without any sharp line of distinction between the fields (fig. 95). The bone marrow showed foci of the same cells with lymphocytes centrally and the plasma cell-like forms in marginal zones (fig. 94). The spleen was slightly enlarged with mixed cell infiltrates in the red pulp, while the white pulp appeared normal. The liver was of normal size but showed sparse periportal infiltrates, mainly lymphocytes. The lymph nodes were also of normal size, but showed a typical picture of macroglobulinemia, described earlier. Here, too, the lymphocytic and the plasma cell-like forms were arranged in a chess-board fashion. All the lymph nodes showed abundant atypical blastic forms but they were diffusely scattered and without any HL-like proliferations.

This case thus resembled mainly the "pulmonary" type of macroglobulinemia. The presence of components of IgG and IgA-nature was a remarkable finding. All had kappa light chains. The chess-board-like pattern of the distribution of the lymphocytes and plasma cells was very distinct and in the bone marrow foci plasma cells always formed marginal zones around the lymphocytes. It appears reasonable to assume that the lymphocytes differentiated into plasma cell-like forms and were thereby displaced towards the periphery of the foci. In this process they possibly changed their production of heavy immunoglobulin chains.

DISCUSSION OF MACROGLOBULINEMIA MATERIAL. Analysis of the bone marrow smears can evidently detect most typical cases of macroglobulinemia simply from their cytological characteristics. As mentioned elsewhere in this publication, a cytologic picture resembling that of macroglobulinemia was occasionally seen in cases with another type of immunoglobulin production (case 413/61). Such cases are presumably rare. Further, it is obvious that cases with clinical macroglobulinemia may have a cytologic picture differing from the classical one (99/62). Further, it is clear from what was said above that cases with large macroglobulin components and a tissue picture of classical macroglobulinemia may have leukemic disease resembling CLL (1224/70) and that clinically characteristic macroglobulinemia can develop into malignant lymphoma with quite another picture of the tissue (777/68).

Is Waldenström's macroglobulinemia, then, an entity distinguishable from other lymphoproliferative conditions? It is obvious that on electrophoresis small macroglobulin components may occur in lymphoproliferative diseases which do not resemble classical Waldenström's macroglobulinemia clinically. But if one limits the diagnosis to cases with macroglobulin components with a higher concentration, the situation will be different. It has been recommended to set the limit at about 1.5 gram/100 ml (see e.g. survey in 44). In the present material, however, there were cases where the first determination showed concentrations of less than 1 gram/100 ml (891/69, 0.74 gram/100 ml, later increasing), but where the morphology was that of classical macroglobulinemia. Cases with macroglobulin components of this size may thus be examples of true incipient macroglobulinemia or of cases with lymphoproliferative disease of some other type. If the concentration of the component at the time of diagnosis is more than 1.5 gram/100 ml, the disease will most often be of morphologically macroglobulinemia type. In treated cases the concentration of the component may, of course, fall again with preservation of the picture of the tissue. Presumably, the macroglobulin is produced by the plasma cell-like forms in the bone marrow and probably also elsewhere in the tissues. Should these cells be regarded as neoplastic or are they reactive cell forms with production of antibodies against some unknown agent? If the immunoglobulin-producing cells are tumour cells, it would seem remarkable that the concentration of the M-component can fall in advanced disease with increasing infiltration of pathologic cells, or when the patient is affected by obviously malignant cell proliferation. A similar situation may be seen in multiple myeloma, however, when the monoclonal immunoglobulin component may decrease in concentration in spite of a rapidly expanding tumour mass. The situation also can be compared to the few published cases of CLL, where leukemia disappears with the appearance of HL (see later). Immunofluore-

science studies of the sarcomatous growths in cases of macroglobulinemia reported in the literature argue against the production of immunoglobulin in such tumour cells (see chapter 1). The development of clearly malignant tumours terminally does not necessarily mean that the disease should be regarded as malignant from the beginning. Compare, for example, the well-known development of malignant lymphoma in immunodeficiency states. In my opinion, however, some of the features referred to above suggest that the disease should be regarded as a low grade malignant process from the very beginning. Case 1224/70 obviously fills all criteria for leukemia and may thus by definition be regarded as a malignant condition. Since the picture of the tissue was of macroglobulinemia type and not of CLL-type, I feel, as previously pointed out, that it is probably a question of a true leukemic macroglobulinemia. Probably only the lymphatic cells have a strong tendency to be released into the circulation while the plasma cells and the blast-like cells are bound to the tissues. A similar situation is seen in LLD-1 or LLD-3, where the blood morphology may be mainly mature, while the tissue morphology may contain a high percentage of immature cells. The morphologic picture of a tissue may therefore characterise the disease better than the blood picture. Another point arguing for the malignant nature of the disease is the atypical, blast-like forms in the tissue infiltrates which are always found, though in low percentage, in early stages. They are probably analogous to IF-cells in CLL. It is probably these forms of cells that cause sarcomatous growths in the terminal phase. The sarcomatous transformation seen in 2 of these 9 patients may have had a similar relation to these immature cells as HL had to IF-cells in LLD-1. If the IF-cells can become HL-cells having lost the capacity of lymphocyte production, it is not unreasonable to suppose that on transition to HL the immature cells in macroglobulinemia lose their ability to produce macroglobulin-producing daughter cells. The lack of demonstrable production of macroglobulin in tumour cells is therefore no proof against the assumption that the cells are related to the initial lymphocytic infiltration.

The nature of the immature cells could not be studied more closely because of lack of suitable material. They resemble IF-cells, but have not the focal distribution of the latter and are more atypical in that the shape and chromatin structure of the nuclei are more irregular.

The occurrence of cases with several M-components suggests that the disease attacks lymphocytic cells in transformation. V. 434/71 showed a very marked plasma cell differentiation and also had immunoglobulin components of both IgG and IgA-type. The occurrence of cases with macroglobulinemia-like morphology but with M-component of another type, might perhaps be explained as a condition where the transformation is so rapid that the macroglobulin-producing stage of the cells' life is too short for any measurable concentration of macroglobulin to appear in the plasma. This assumption may be strengthened by the absence of cells intermediate between lymphocytes and plasma cells in those latter-named conditions.

The above speculations are not well founded because of the smallness of the number of cases in the series. Despite the interest in macroglobulinemia and the numerous publications on this disease there is hardly any published series of cases

studied morphologically on different occasions during the course of the illness, and further such series are desirable in order to get a better grip on the nature of the disease, as it is evidently not uncommon that a change from "benign" to "malignant" takes place, both clinically and morphologically.

Clinically characteristic cases of macroglobulinemia have some morphological resemblance to LLD-3 in the nodes but the cytological picture is characterised by a series of cells with a smooth transition from lymphocytes to plasma cells. In LLD-3 such intermediate forms are not seen and the lymphocytic cell component is considerably more atypical. Lymph node tumours are not a feature of macroglobulinemia, at least not in the early phases. Macroglobulinemia appears to be primarily a disease of the bone marrow.

See further the discussion on nomenclature in chapter 12.

Chapter 8

THE IMMATURE CELLS IN CHRONIC LYMPHATIC LEUKEMIA

1. IF IN BIOPSY MATERIAL. The investigation was confined to lymph node specimens. Sections of the bone marrow were available in only a few cases. I have, however, a large number of bone marrow sections from cases of CLL that are not included in this material. Judging from personal experience, IF are rarely demonstrable in such sections and thereby confirm experience from the necropsy material (see below). In the marrow the immature cells are most often diffusely distributed. The immature cells described in bone marrow smears, however, cytologically resemble IF-cells in the lymph nodes and are presumably of the same nature (figs. 8, 9).

IF in lymph nodes vary widely in size and number. They are often detectable even under low magnification (fig. 1) and are always seen throughout the node with no difference between the peripheral and central parts. They are often of uniform size, but can coalesce to form larger areas of immature cells. Sometimes, however, IF are small and one must search for the typical cells under high magnification. Occasional immature cells are found single in the mature parts. The IF are richly vascularised. Sometimes one sees a wide capillary centrally in the IF, sometimes a somewhat wider vessel of precapillary dimensions. Longitudinal sections of such vessels will occasionally show IF as vessel sheaths over long areas.

IF contains at least 4 different types of cells (like LLD-2, which in every respect consists of the same tissue as IF, though it is not focal but involves the entire node):

1. Mature lymphocytes. The percentage of such lymphocytes varies. The larger the IF the fewer such lymphocytes, but the smallest IF are so to say only a concentration of immature cells among mature lymphocytes and not well outlined foci.

2. Prolymphocytes. They are generally the dominating cell.

3. Single very large cells, with a diameter of at least 4-5 lymphocytes with abundant, strongly basophilic cytoplasm and a nucleus without chromatin condensation and with one or several large nucleoli staining dark blue with Giemsa (figs. 2, 182). These cells are very rare and far from every IF in every plane of the section contains such examples. They increase in abundance with the size of the IF. They are hereinafter called IF-1 cells.

4. The cells described earlier (chapter 4) and illustrated for example in figs. 2, 4, 148 and 182. They are intermediate in size between IF-1 cells and prolymphocytes. The nucleus shows a certain chromatin condensation of lymphocyte-like type, but always contains one large, often centrally situated nucleolus staining light blue with Giemsa. They are hereinafter called IF-2 cells. Mitotic figures are seen in IF-1 and in IF-2 cells, and in prolymphocytes.

These 4 types of cells, which I am inclined to interpret as 4 generations of the same form of cell, are fairly well distinguishable from each other morphologically

but there is, of course, a certain variation of the different forms of cells, which occasionally makes it uncertain whether a given cell is IF-1 or IF-2 or whether it is IF-2 or prolymphocyte (see further chapter 10).

Are IF specific of CLL? It is clear from the preceding sections that IF occur practically only in cases with a leukemic blood picture. A single case in this series showed suspect IF without clear leukemia of the blood (902/71 in chapter 6). This was probably a very early and certainly subclinical disease. Practically all of the cases with IF thus had the blood and bone marrow picture of CLL. Those cases called LLD-3 had, according to definition, not IF. Many of them were aleukemic and they were cytologically more atypical than cases with IF. Whether one should regard IF as exclusive of CLL is thus a question of definition. Leukemic LLD-3 may resemble the less atypical LLD-1 hematologically, and morphologically intermediate cases suggest a close relationship. But there are differences clinically, if one regards the cases as groups. I have chosen to regard LLD-1 as representing CLL, and I have retained leukemic LLD-3 as a special group, though I am well aware that many hematologists and possibly with equal right, would call both types variants of CLL. Typical IF are thus seen, according to this point of view, only in CLL. But it is beyond doubt that also LLD-3 contains immature cells resembling IF-cells, though they do not form the characteristic foci of CLL. Aspirates, as pointed out earlier, do not show the clear division of generations in these cases, and the mature cells are partly atypical.

An essential question is whether IF are constant structures or whether the picture can change between different nodes and from one time to another. It is difficult to give a clear-cut answer to this question. IF were sometimes not detectable in necropsy specimens, even if the biopsy specimen of a lymph node in the same site had shown such foci. This probably had a technical explanation, *viz.* it was due to autolysis. One must thus resort to biopsy specimens. Of the LLD-1 cases, there was more than one lymph node biopsy specimen with a picture of LL in only 2 cases, both of which clearly had IF on both occasions. In one of the biopsy cases 4 lymph nodes adjacent to each other were removed on the same occasion. All of them had IF. In 2 of the LLD-3 cases there were later biopsy specimens that showed a picture of LL. IF were not seen. None of the biopsy cases of LLD-3 showed IF in necropsy specimens. The findings in these few cases thus suggest constancy. In those cases where repeated bone marrow smears had been obtained it was meaningless to try to assess the percentage of immature cells with accuracy owing to the varying dilution with blood. I would assume that IF in lymph nodes and the percentage of immature cells in the bone marrow can vary from time to time though the material described provided no acceptable documentation. But both phenomena are probably always present to some extent in CLL.

The amount of IF does not appear to be directly related to the value of WBC in the peripheral blood. When the extent of IF in biopsy specimens was graded subjectively into 3 groups, the following picture was obtained (fig. III).

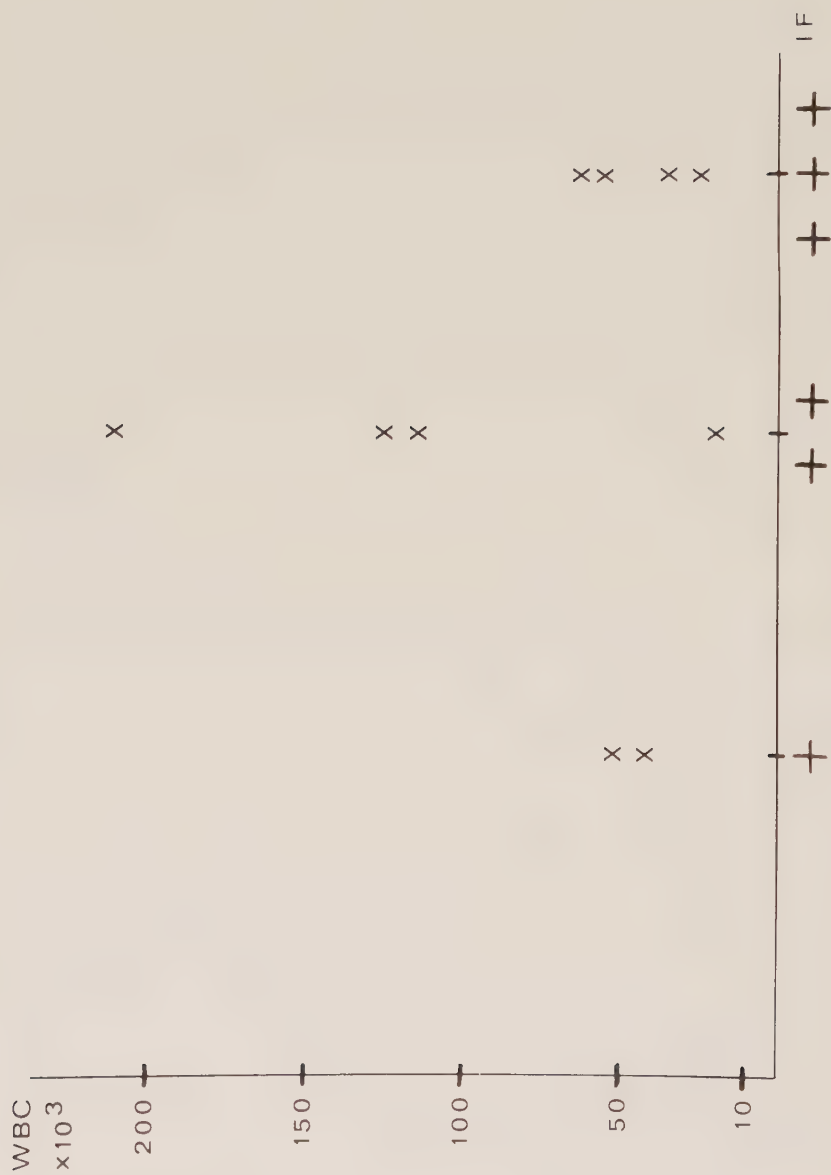


Fig. III. Extent of immature foci in lymph node biopsy specimens from untreated patients.

Thus, there was no direct relation between the distribution of IF in a given lymph node and the WBC. However, owing to the uncertainty of the representativeness of the biopsy specimen for all lymph nodes in the body, this can hardly be taken as evidence that there is no such correlation. Only biopsy specimens of patients who had not been treated are included in fig. III. In 3 cases treatment had been started before biopsy. One of them that had received radiation to the region in question had the most extensive IF in the series and one lymph node with a picture in parts resembling LLD-2 with coalescent IF and a focus of HL (figs. 146, 152). The WBC at the time of biopsy was 25,000. Two of the patients had received cytostatics and in one of them the WBC was normal, the other had severe leukopenia, but both had IF ++.

2. IMMATURE CELLS IN THE BONE MARROW. Seven of the bone marrow aspirates in group 1 had immature ++. They ranged from 20,000 to 600,000 in WBC at the time of aspiration with a mean of 190,000. In the 35 + cases it ranged from 11,000 and 295,000 (mean 85,000). The difference was statistically not significant. Also a number of patients in both series had been treated for a varying period before examination, which makes evaluation difficult.

The cases in the bone marrow series with immature +++, thus group 2, had at the time of aspiration a WBC of the same level as in group 1, with an average of 97,000 if the aleukemic patient be excluded. As previously mentioned, these patients might have had a greater tendency to reach very high WBC, but the difference was by no means striking.

It is thus not possible to correlate immature cells in lymph nodes or bone marrow with the level of the WBC in the peripheral blood in this material.

3. IMMATURE CELLS IN THE PERIPHERAL BLOOD. If all patients with ++ or +++ in the peripheral blood (thus from groups 1 and 2) were pooled, there would undoubtedly be a concentration of cases with very high maximal values of WBC, with an average of maximal values of 328,000. Of all these 10 cases, 6 had on some occasion more than 150,000. The difference from cases with + in the peripheral blood was, however, not striking at the time of the first investigation, but only regarding the maximal values recorded.

"Prolymphocytic leukemia" according to Galton et al. (19) is probably the same as the cases in my series with a high percentage of immature cells in the peripheral blood (+++ or ++). Galton et al. defined their cases on the basis of the blood picture and not on that of the bone marrow. Broadly speaking, the series resembled each other. Galton et al. wrote that splenomegaly was typical of their cases. In my cases it was impossible in retrospect from the clinical records to grade the enlargement of the spleen in an exact way, but in at least 5 of 9 cases the spleen was described as very large but in 3 it was not palpable (1 case could not be judged because the spleen was covered by colonic cancer). But the lymph nodes were markedly enlarged in 6 of my 10 cases, while Galton et al. reported that enlargement of the lymph nodes was not striking in their series. Enlargement of organs at necropsy is difficult to evaluate because of the effect of earlier treatment. The average weight of the spleen in my cases at necropsy was 1,020 g (one excluded because of scarring after infarction) (Galton et al. 1,383 g). In the bone marrow series the cases with + in the

peripheral blood (27 cases) had, on the average, a spleen weight of 600 g. Corresponding liver weights were 2,000 g (Galton et al. 2,445 g) and 1,910 g. It is, however, not very meaningful to compare the values because several of the largest spleens had been irradiated and some showed HL. The findings, nonetheless, suggest a relationship between the prolymphocytic leukemia of Galton et al. and cases with ++ and +++ in the peripheral blood in my series. Those patients who died in the series of Galton et al. had survived, on the average, 12 months. The patients in my series survived, on the average, 30 months, while the + cases survived, on the average, 49 months. Here too, comparisons are unreliable. It is not possible to gather from the report of Galton et al. whether all the patients died from the disease, and therefore all the patients in my series were included in the above calculation irrespective of the cause of death, but if only those patients who had died from the disease were included the difference would nevertheless be similar - 30 (8 cases) against 53 (17 cases) months. The cases of Galton et al. had very high WBC, like those of my series with a high percentage of immature cells.

The difference between the series of Galton et al. and mine may perhaps be due to a difference in selection. My group ++ was admittedly very broad, but the quality of the smears did not permit any precise grading of the number of immature cells. The cases of Galton et al. consisted, according to the description, of cases with a majority of immature cells, but the authors wrote that all the cases had a varying percentage of small lymphocytes, too. The comparison between these 2 series may therefore be justified.

These findings placed in relation to those mentioned earlier in group 2 in the bone marrow series would thus suggest that the aggressiveness of the disease was better correlated with a high percentage of immature cells in the peripheral blood than in the bone marrow and lymph nodes. One might speculate that this was due to the blood picture being more representative of the situation in the organism as a whole than single bone marrow or lymph node specimens which represent very small volumes of tissue, while the blood picture might so to say be the synthesis of the entire lymphatic system. This would, however, mean an oversimplification because LLD-2 with widespread disease may be aleukemic.

I feel that prolymphocytic leukemia and LLD-2 are the same process, but possibly that the hematologic picture of prolymphocytic leukemia may occur also in the picture of the lymph node of LLD-1 with large IF. Further I feel that LLD-1/CLL and LLD-2/prolymphocytic leukemia are variants of one and the same disease. Are these variants, then, from the beginning constant in type, or is the relation between them comparable to that between chronic myeloid leukemia and terminal myeloblastic leukemia? I cannot give any clearcut answer to this question. The shorter survival of LLD-2/prolymphocytic leukemia might suggest that it is the final phase of LLD-1/CLL. On the other hand, there are cases like 671/66, which showed a picture of aleukemic LLD-2 already 148 months before death. It is not probable that this patient had previously had CLL. Clinically, CLL does not seem to change in character and develop into a hematologically more malignant final phase except in rare cases (it is most often a question of HL when the patient clinically deteriorates rapidly in the end phase). On the other hand, during the late phase of the

disease the patient's blood and bone marrow may be examined less often and at any rate prolymphocytic leukemia is uncommon, compared with classical CLL. The few cases of "blastic transformation" of CLL reported presumably represent transition to prolymphocytic leukemia. One might suspect that prolymphocytic leukemia (like myeloblastic leukemia) may occur both as a primary disease and as the final stage of chronic leukemia. The transition of CLL to HL must be much more common than this development, however.

4. IF IN NECROPSY SPECIMENS. As previously pointed out, necropsy specimens are not always satisfactory for classification of diffuse lymphomas because of shrinkage of the cells and autolysis. It is sometimes impossible to find clear-cut IF in necropsy specimens even if such has been found in biopsy specimens of lymph nodes from the same site. This might be because IF are inconstant and disappear in successfully treated patients or for some other reason. But much argues against this possibility. In good specimens obtained soon after death and properly fixed it is usually possible to detect IF. Further, as pointed out above, IF do not disappear even after irradiation of the node or successful cytostatic therapy. Every pathologist knows that it may be difficult to demonstrate germinal centers in necropsy specimens of normal lymph nodes. The situation regarding IF may be analogous. In all the cases judged as LLD-1 in the necropsy material suspect IF could be found somewhere in the tissues examined, but they generally had to be searched for and were not easily discerned in most cases, nor were they possible to find in all the tissue blocks examined. However, striking IF-like formations were sometimes seen also in technically unsatisfactory necropsy specimens (figs. 112, 113). This was because they contained large and atypical cells, which were strikingly different from other lymphocytes even in poorly preserved tissues (fig. 114). Only one of the lymph node biopsies contained such atypical cells in the IF, and this was a case where HL was also found in the same node (fig. 147).

The necropsy specimens of the 94 LLD-1 cases were studied in the following way:
 IF-necropsy (IF-n): all cases where the above described foci with atypical cells were demonstrated, but without HL 24 cases
 HL: microscopically clearcut HL 12 cases.

It is apparent from the preceding sections that HL-changes may develop in patients with lymphocytic lymphoma. Also changes resembling those in Hodgkin's disease can develop. For the sake of brevity, in what follows lesions of the latter type are, unless otherwise stated, to be regarded as included in the scope of the term HL, because these changes appear to develop in an analogous way.

Two of the specimens with IF-n showed suspect HL within IF-n but without really convincing HL. One of the HL-cases had only microscopic lesions without any distinct gross difference from other nodes in the case. The other HL-cases had tumorous lesions differing markedly macroscopically from other lesions. The groups thus showed transitional forms.

IF-n. These foci were never seen in all affected tissues of a case. This may perhaps be due to technical factors such as a varying degree of autolysis, but there is no reason to assume that retroperitoneal lymph nodes, for example, should have undergone less autolysis than inguinal lymph nodes and the frequency of IF-n differed markedly

between these sites. IF-n were seen in lymph nodes with the following frequencies:

Retroperitoneal	15 cases
Supraclavicular	14 "
Axillary	12 "
Mediastinal	9 "
Inguinal	7 "

The liver showed IF-n in 6 cases, the spleen in 4 and the bone marrow in 4. IF-n were found in the renal hilar fat tissue in 3 cases and in the renal parenchyma in 1, but in no other parenchymatous organs. In the spleen IF-n were confined to the white pulp and the infiltration in the red pulp showed no such changes (in those cases where it was possible to discern a border between the two tissue components). The changes were more striking in the femoral marrow than in the vertebrae. In those lymphocyte infiltrates that were well separated from each other as in the liver IF-n, when solitary, were always situated centrally and often had exactly the same outline as that of the lymphocyte infiltrate.

When reading the necropsy protocols it was evident that those sites containing the largest lymph nodes had the most prominent IF-n in the sections. It is difficult to demonstrate this objectively because of the inexact grading of the size of the lymph nodes from the text in the protocols. It was also obvious, when examining the sections, that the most striking IF-n occurred in the largest lymph nodes. They tended to be more atypical the larger the node. Also this tendency is difficult to demonstrate objectively because the largest lymph nodes were divided before embedding and the area of the section could therefore not be measured and compared.

Most obvious was the relation between the magnitude of the lymphatic infiltrate and the extent of the IF-n in the liver and spleen. The 4 spleens with IF-n weighed, on the average, 1,400 g, and 2 of them had been irradiated because of their excessive size. It should be stressed that this applies only to cases with IF-n in splenic tissue. When IF-n were seen in the lymph nodes or elsewhere, but not in the spleen, the organ was not remarkably large and this applies also to the liver. The average weight of the spleen in all cases of LLD-1 without IF-n or HL was 410 g. The average liver weight in the 6 cases with IF-n was 2,710 g, for the other cases in the LLD-1 series (without HL), 1,650 g.

Still more striking was the relation in size between IF-n and the individual lymphocytic infiltrates in the liver where the infiltrates in the portal tracts were easy to distinguish from one another. IF-n were never seen in portal tract infiltrates which did not appreciably expand the portal tract and rarely if it had expanded less than about 4 times its diameter. When the infiltrates coalesced IF-n were always seen.

This applies also to the spleen which sometimes showed large lymphocytic nodules without normal splenic vascularity and which occasionally appeared macroscopically as small tumours. These foci always contained IF-n. This situation can be interpreted in one of 2 ways: either IF-n increase in size in large infiltrates, or the infiltrates increase in size because they contain IF-n. In view of the high mitotic frequency in IF-n the latter theory appears more probable. On the other hand, the size of the individual infiltrate is due mainly to the lymphocytes and it is therefore difficult to refrain from assuming that the lymphocytes are formed from the cells

in IF-n.

The 2 cases in this series which had HL-suspected atypia in IF showed these changes in the very large liver (1 case) and in the large coalescent retroperitoneal lymph nodes (1 case). The latter case (1124/63) had at the time of diagnosis 74,000 WBC and 93 % lymphocytes. The patient was treated with triethylene melamine for 6 months and the WBC and the differential count became normal and the enlargement of the lymph nodes decreased markedly. The patient was afterwards hematologically normal for about 7 years without treatment. A bone marrow aspirate during this remission was, however, described as showing the picture of CLL (performed elsewhere, specimen no longer available). In the last year of life the lymph nodes again began to grow and the patient developed a marked tendency to infections and he died of pneumonia 94 months after the diagnosis without having become leukemic. Apart from this patient, all those in the series were leukemic just before death (23 cases). In 18 the WBC was recorded in such a way that one could judge the terminal tendency. In 12 the WBC tended to fall, in 6 to rise, but not dramatically. Of the 24 IF-n cases, 18 had on some occasion received specific therapy. Six had received radiotherapy on some occasion, generally also some other specific therapy. Combined corticosteroid and cytostatic therapy was the most common treatment, in 10 cases. Six of the cases had never been treated with radiation, cytostatics or corticosteroids.

Twenty-one of the 24 patients who had IF-n had died of lymphoma compared with 24 of 58 in the CLL-group without IF-n or HL. In other words, among those who died of lymphoma (without HL) IF-n were found in 21 of 45 (47 %), but in those who died from some other cause IF-n were found in only 3 of 37 (8 %).

This might suggest that IF-n indicates a more malignant type of disease. The average survival of these patients was, however, 46 months while the average survival of the entire CLL-material without IF-n or HL was 32 months. It would appear that the most reasonable interpretation of this is that IF-n are a sign that the disease had approached its natural terminal phase.

The LLD-1 material (94 cases) included 12 M-components in 78 patients examined with electrophoresis (15 %). One of them had IgG-myeloma, and was therefore excluded. Probably all the others (14 %) were of IgM-type (the 2 cases of IgG in the bone marrow group 1-3 were not included among the 94 LLD-1 cases, see later). Of 11 M-components, there were 6 among the 24 patients who had IF-n and 3 among the 12 HL-cases. In other words the group with IF-n had 25 % with monoclonal immunoglobulin production and the HL-group also 25 %. In the rest of the CLL-cases examined (without IF-n or HL) 5 % (2 of 42) had monoclonal immunoglobulin production. In other words, M-components were 5 times more common in patients with IF-n or HL than among patients without these changes. Does this mean that patients who develop HL or IF-n differ in character from the others? Not necessarily. Of these 9 cases (HL + IF-n) only 2 had M-components already at the time of the first electrophoresis, in 7 it occurred later. In many cases it was not possible to know exactly when it appeared because there were only a few examinations, but the electrophoresis at which it was first observed date from the time 1 - 12 months

before death. The method of electrophoresis had been modified during the study period by replacing paper by agarose. The increased sensitivity of the diagnosis of M-components thereby obtained may be the cause of the change in only one case. In the patient where the M-component appeared 12 months before death its concentration was doubled successively until just before death. The remainder had been examined only once or twice so that the tendency was difficult to judge. One of the two patients who had his M-component initially was not further controlled, in another the concentration remained unchanged during the rest of life, 28 months. The appearance of an M-component in a CLL-patient may be an omen malum quoad vitam and may be a sign that HL is under way.

Chapter 9

MALIGNANT LYMPHOMA OF HISTIOCYTIC TYPE IN CHRONIC LYMPHATIC LEUKEMIA AND OTHER DIFFUSE LYMPHOCYTIC MALIGNANT LYMPHOMAS

Necropsy revealed Hodgkin's disease in 2 cases and HL in 10 of the LLD-1 series. Unless otherwise stated, the 12 cases are treated together below.

Of the 2 subjects with Hodgkin's disease, one was a 77-year old man and one a 67-year old woman. Of the 10 HL-cases, 7 were men and 3 were women, aged 50 - 82 years at death (mean 71 years).

One of the patients (136/58) had died from complications of myelomatosis 21 months after the diagnosis of CLL; the others, from the lymphoma, 15 - 180 months after the diagnosis of CLL (average 60 months).

In 2 of the subjects HL had been diagnosed intra vitam 4 months and 15 months, respectively, before death. The latter had sought medical advice because of a nasal polyp, which at biopsy was found to be HL, but he was leukemic at that time. In the others CLL had been diagnosed long before the appearance of symptoms of HL. The time of onset of the HL-changes was naturally uncertain. In 669/73 a gingival tumour suddenly appeared. It proved to be HL and he died within 4 months from widespread HL. 136/58 was examined with lymph node biopsy 8 months before death and then had LLD-1 with IF +++. At necropsy he had only HL in the same lymph node site, which had thus presumably developed in the meantime. In the other cases no morphologic data were available to date the onset, but HL had probably started from 1 - 12 months before death. They were characterised by very rapid general deterioration. All except 83/64 (HL in stomach) had bouts of fever for several months before death. At least 2 patients had continuous subfebrility, interrupted by spells of high fever without evident cause. All complained of extreme tiredness. The organ involved by HL at necropsy had grown rapidly in all the cases where examinations thereof had been recorded.

In 83/64, who had gastric HL, the clinical picture was interpreted as rapidly growing gastric carcinoma. The exact time of onset of the symptoms was uncertain, but it was probably much less than 1 year before death.

In 831/70 the initial symptom was swallowing difficulties, and oesophageal carcinoma was suspected. In a few months a large tumour grew through the sternum and ulcerated up through the skin and the patient died about 6 months after the onset of symptoms.

The cases with Hodgkin's disease showed a similar terminal course. About 1 year before death general deterioration rapidly appeared with fatigue, sweating and spells of fever, in retrospect characteristic of Hodgkin's disease. Both showed a rapidly growing liver and spleen with pain, especially over the liver. Both had the most widespread changes of Hodgkin's disease in the liver or spleen.

All 12 patients were leukemic at the time of the diagnosis of CLL, WBC ranging between 11,000 and 211,000. All had on some occasion more than 20,000 WBC. Biopsy specimens had been obtained of the lymph nodes of 4 cases. IF were graded in these in the following way (figures in brackets denote number of months between first biopsy of lymph nodes and death):

1 case	+	(57 months)
1 case	++	(70 months)
2 cases	+++	(19 and 12 months).

One of the +++ cases had been biopsied again 8 months before death. The findings were the same as on the previous occasion.

The bone marrow had been examined in 9 cases. The amount of immature cells in the bone marrow smears was graded as follows:

7 cases + (8, 14, 20, 35, 40, 47 and 109 months)

2 cases ++ (24 and 48 months)

One had ++ in the blood: the remainder +.

The percentage of immature cells in the bone marrow did not appear to be directly related to the subsequent development of HL, which appears reasonable because of the relatively unusual occurrence of HL in this organ. The 2 cases with IF +++ in the lymph node biopsy developed HL more rapidly than the others, but the number of cases was too small to claim that +++ cases had a greater risk of developing HL.

Six of the patients had received specific treatment before the development of symptoms referable to HL; one had received radiotherapy, 4 cytostatics, 6 corticosteroids, in various combinations. Five had never received radiotherapy, cytostatics or corticosteroids. Their average survival time was 35 months (15 - 48), including the terminal phase. Those treated survived, including the terminal phase, on the average, 81 months (30 - 180). In 1 case the treatment was uncertain because the records were incomplete. Thus, nothing suggested that the treatment had caused or accelerated the development of HL. The 2 HL-cases diagnosed *intra vitam* were treated by irradiation of the primary manifestation and with a good local effect, but the patients soon died despite treatment (within 4 and 15 months) and necropsy revealed generalisation.

There was no characteristic hematologic reaction pattern to treatment of CLL in the cases which eventually developed HL. One showed successively increasing WBC despite therapy; one had varying but high values the whole time; one unchanged, moderately increased values (15 - 25,000); 3 showed normalisation of WBC after treatment, including 2 in whom the values fell to slightly leukopenic levels with absolute lymphopenia and one in whom the WBC later remained normal, but with absolute lymphocytosis. In only one (961/61) of these 3 did the WBC remain normal until death, the others had recurrences. Of the 5 not treated, 4 showed successively increasing values and 1 could not be judged in this respect because the diagnosis of HL had been made at the same time as CLL and the WBC had afterwards fallen during radiotherapy.

All the patients except one (961/61, see above) were leukemic just before death. It is, of course, difficult to date the onset of the HL exactly, but most of the patients had deteriorated abruptly in association with growth of the affected organ.

This was followed by a falling tendency of the WBC in 3, no change in 4, a tendency to rise in 4, and no adequate recording for evaluation in 1 of the cases. Two of the 3 in whom the values tended to fall received radiotherapy. Thus, the hematologic findings did not suggest that the HL-cases were different from other CLL-cases. Such an "extinction" of leukemia at the onset of HL described in the literature (see discussion in 73) was rare. The only case (961/61) with such a tendency is illustrated in fig. IV.

The disappearance of lymphocytosis in this case was probably due to radiotherapy.

In all the cases the bone marrow showed a varying degree of lymphocytic infiltration at necropsy. All showed also residual leukemic changes in other organs. There was thus no reason to assume that the HL-changes eliminate or replace leukemia. This may possibly take place if the entire lymphatic system including the bone marrow is destroyed by HL, but a patient rarely survives long enough for such destruction to occur.

All the patients had been examined with electrophoresis on some occasion. The immunoglobulin values showed the following picture (myeloma case excluded):

	Low	Normal	High
Early	5	4	0
After probable start of HL	8	0	1

The patient with a late high value had not been examined before. Three showed M-components:

31/67 was a man, aged 77 at death, who had fallen ill 180 months before death. Electrophoretic examination on 4 occasions during his disease showed low immunoglobulins without M-component. The latest electrophoresis 2 months before death showed a plasma component, IgMK 0.30 gram/100 ml with background immunoglobulin unchanged. At necropsy he exhibited characteristic changes of Hodgkin's disease.

961/61 was a man, aged 66 at death, who had fallen ill 47 months earlier. Three electrophoretic examinations during the course of the disease had shown low immunoglobulin levels without M-component. Twelve months before death (beginning symptoms of HL) electrophoresis had revealed an M-component in β -2 (0.31 gram/100 ml). Ten months later the concentration was 0.58 gram/100 ml. The background immunoglobulin was falling. Necropsy showed HL.

1298/65 was a woman, aged 50 at death. She fell ill 30 months before death. Electrophoresis showed low immunoglobulin values in the plasma. The urine contained a small Ig μ -component which persisted at several later examinations, but was not quantified. The plasma immunoglobulin was slightly falling.

Three of 12 cases thus had an M-component in addition to one with IgG-myeloma. Three had not been examined after onset of HL-symptoms.

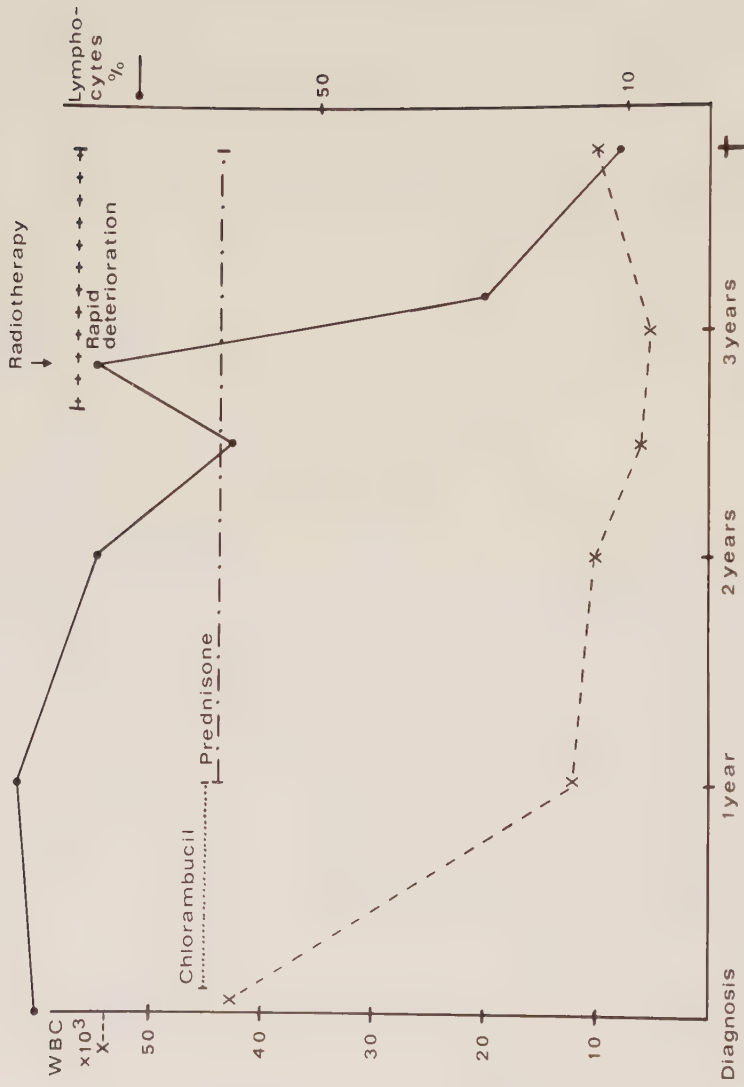


Fig. IV. Case history 961/61.

TOPOGRAPHY AND PATHOLOGY OF HL-LESIONS. Symptomatic HL-lesions often appeared in extra-lymphatic sites, especially in the throat and air passages. Eight of the HL-cases (but none of the cases with Hodgkin's disease) had on some occasion extra-lymphatic tumours. 829/69 and 961/61 had a tumour in the paranasal sinuses and the base of the skull as presenting symptoms. 831/70 had a tumour in the anterior mediastinum and 669/73 had a gingival tumour as initial symptom. Four had pulmonary lesions at necropsy which were situated peripherally and did not appear to have originated from peribronchial infiltrates. They might, however, have originated from subpleural infiltrates.

The regions of the throat and airways appeared to be responsible for an unproportionally large part of the symptomatic HL-lesions also in other groups. 437/67 in group 1-3 also developed HL of the throat and base of the skull. 451/61 (LLD-4) developed HL of the throat and tonsils and 290/70 (LLD-3) of the nasal mucosa.

The changes, however, sometimes developed first in other organs. 83/64 had a large solitary gastric tumour (fig. 126), but did never develop HL-changes in the lymphatic system. In 2 (136/58 and 1434/64) there were never extra-lymphatic lesions. All others had not only extra-lymphatic lesions but also HL-changes in the lymphatic system.

At necropsy the changes of lymph nodes were situated as follows (HL + Hodgkin's disease):

Supraclavicular	8
Mediastinal	7
Retroperitoneal	6
Axillary	5
Inguinal	2

The higher frequency of changes supradiaphragmatically was probably related to the concentration of the changes in the airways.

The spleen showed changes in 3 cases (weight 850, 1370 and 1900 g). Multiple pea-sized lesions were seen macroscopically in all 3 cases.

The liver showed changes in 7 cases (weight 1620 - 2980 g, mean 1990 g). The smallest liver and spleen had been irradiated because of pain (Hodgkin's disease) and had markedly decreased in size before death. Six of the 7 had grossly visible multiple lesions, ranging from a diameter of some millimetres to about 3 x 3 cm. All the lesions in a given case were of roughly equal size. All the smaller lesions of HL and Hodgkin's disease were surrounded by lymphatic tissue, like IF-n. They often had the same external contour as the lymphatic infiltrate in which they were situated. In the largest lesions all pre-existing structures had been destroyed.

Only in 3 cases did the bone marrow show HL-changes, always microscopic. 136/58 had widespread, osteolytic myeloma infiltration, while the rest of the marrow showed lymphocytic infiltration with single, very small HL-foci. 1298/65 had small HL-foci in the femoral marrow, while the vertebral bodies showed a picture similar to that of LLD-2 with fibrosis but without HL. 31/67 exhibited fairly widespread Hodgkin's infiltration of the vertebral bodies but without bone destruction or macroscopic lesions.

The involved lymph nodes were always markedly enlarged and, with one exception (38/73), had a sarcomatous appearance with confluent aggregates with grey-white cut surfaces and often necroses. In 38/73 the picture of the lymph nodes involved differed only little from that of the others in the case except that they were larger. In this case the changes had partly the character of HL in IF-n. The patient had, however, also tumorous HL in the lungs. In 6 there were areas with a picture of LLD-1 with IF-n in other parts. None had HL in all lymph node sites. In the necropsy specimens the HL-involved lymph nodes were nearly entirely affected, probably because the pathologist had selected large nodes for microscopy. Biopsy of 829/69 showed a pea-sized HL-focus in an otherwise lymphocytic node (fig. 152). The HL-focus was fairly well demarcated but surrounded by coalescent IF (fig. 146).

In 4 cases the clinical symptoms at the onset of HL suggested a solitary extra-lymphatic tumour. Presumably it is rarely a question of such a tumour, however. The short survival time despite successful local treatment combined with widespread lesions at necropsy suggest that the process had been widespread already before HL had been diagnosed. Especially the picture of the liver lesions suggested multiple, simultaneous origin from IF-n in this organ. It seems probable that a transformation into HL can occur systemically, but that lesions in the throat are most apt to produce early symptoms. Cytostatic therapy rather than local radiotherapy might possibly have retarded the course or offered palliation. On the other hand, there were cases with solitary lesions and in such cases radiotherapy is indicated in spite of the risk that similar changes soon may develop elsewhere. The most important sites of IF-n and HL seemed to be the central lymph nodes and liver. The changes were seen less often in the peripheral nodes and spleen, and it is remarkable that the bone marrow was not involved more often. Gross or destructive lesions were never seen in the bone marrow and microscopically only very small changes except in 31/67 with Hodgkin's disease. The bone marrow is the least rewarding organ to examine in suspect transformation. Rapidly growing organs should, of course, be examined first, lymph nodes, liver or spleen. Fine needle aspiration biopsy is probably sufficient to obtain a provisional or firm diagnosis of transformation.

Clear HL (+ Hodgkin's) changes developed in 12 of 94 (about 13 %). It is clear from what was said above that it is reasonable to assume that all cases with IF-n were really "pre-HL" and if so, 36 of 94 in the series would thus have HL or "pre-HL" at necropsy, i.e. about 38 %. It might be of interest systematically to examine CLL-cases which appear to be in the terminal phase, with respect to electrophoresis, immunological status etc. The possibility of obtaining cells for morphologic and cytochemical studies by fine needle aspiration biopsy should also be considered.

HISTOLOGY OF HL-LESIONS. The 2 cases of HODGKIN'S DISEASE will be considered first.

31/67 showed widespread changes in the lymph nodes. The liver contained both large and small and sometimes coalescent, lymphatic infiltrates in the portal tracts. The larger infiltrates showed lesions characteristic of Hodgkin's disease (fig. 116). They were always surrounded by a brim of lymphocytic tissue which had the same outer contour as the foci of Hodgkin's disease in the center (fig. 115). The largest

lymphocytic infiltrates had several small foci of Hodgkin's disease, often symmetrically situated and always with a preserved lymphocytic margin. The foci of Hodgkin's disease showed characteristic Reed-Sternberg cells, macrophages (fig. 117), plasma cells, eosinophilic leukocytes and fibroblasts as well as fibrosis and small necroses. The changes had partly a granulomatous appearance and were clearly Hodgkin's disease of mixed cellularity type. The changes in the lymph nodes were generally of the same appearance but partly of lymphocyte depletion type, as in the bone marrow. The surrounding bone marrow showed a picture of CLL like some of the lymph nodes.

692/66 showed changes of Hodgkin's type only in the liver and spleen, while lymph nodes and bone marrow showed a picture of CLL. Lymph nodes and liver showed prominent IF-n. The spleen (1370 g) contained abundant grey-white foci the size of a pea, which macroscopically were well outlined against the surrounding splenic parenchyma. They were microscopically built up of mainly polymphocytes. Among them there were smaller foci of histiocytes with phagocytosis of erythrocytes and lymphocytes, and Reed-Sternberg cells (fig. 118), but no plasma cells or eosinophilic leukocytes and no fibrosis. The changes in the liver were of the same type (fig. 119). Also these changes were grossly tumorous and grey-white. The diagnosis of Hodgkin's disease was thus based here on the Reed-Sternberg cells and histiocytes, but the environment was not typical of Reed-Sternberg cells.

THE 10 CASES OF HL PROPER differed from one another in appearance. In 38/73 the lymph nodes showed no gross signs of HL, but microscopically all lymph node sites except those in the groins exhibited large, coalescent IF-like foci with pictures which in large parts must be interpreted as HL, and pulmonary HL-foci, 1 cm or more across. The lymph nodes contained transitional forms between IF-1-cells and HL-cells with abundant cytoplasm and large nucleoli. The picture resembled that of "immunoblastic sarcoma" (42).

Most of the cases in the series had areas of this type. Besides the above mentioned case there were 6 of mainly this appearance, but with considerable individual differences: 83/64 (gastric) showed considerable variation in cell size and the cytoplasm was often sparse. 1434/64 (fig. 134), 1298/65 (figs. 121 - 125), 829/69 (figs. 152 - 160), 831/70 (figs. 127, 128) and 669/73 (figs. 144, 145) were similar in that they all had mainly round cells of roughly uniform size, but a number of very irregular nuclei and cells with long processes were always seen and always a small percentage of lymphocytes among the tumour cells. The nucleus always showed a certain condensation of the chromatin, often peripherally in a way resembling what is seen in IF-cells, but sometimes of coarser and irregular type, which gave the nucleus a plasmocytic appearance (fig. 154). Large nucleoli were often seen, but not always. Mitotic figures were numerous in all the tumours in the HL-group. A large percentage of dying or dead cells were always seen in the tumours, often phagocytosed in histiocytes (figs. 155, 156). Phagocytosis was always seen in these tumours, yet it was generally easy to see that this was not in neoplastic cells. The lung tumours never contained carbon pigment in HL-cells, but they did in reactive histiocytes.

Three cases were of more special type.

Case 42/65 had tumours in the liver with lymphocytic predominance but with

abundant, very large atypical cells, often with several nuclei and giant nucleoli, and the picture showed considerable similarity to the changes seen in Hodgkin's disease, but typical Reed-Sternberg-cells were never seen (fig. 132). The lymph nodes showed unique changes (lung hilus, supraclavicular fossa, paraaortic). The parenchyma contained small foci of the "immunoblastic sarcoma-type" described earlier (fig. 130). They broke out into the lymph node sinus and the cells spread along and within the sinus (figs. 129, 131). The cellular picture was polymorphous and of "histiocytic" appearance. Many cells appeared to be atypical, fibril-associated sinus endothelium, others free sinus histiocytes but all atypical, sometimes bizarre. Many of the cells in the sinus contained lymphocytes. The lymphocytes were sometimes degenerated, but often they appeared to be vital and the cytoplasm of the large cells contained suspect lymphocytic mitotic figures. One might consider the possibility that the included cells represented a form of emperipolesis, rather than phagocytosis.

This patient also had pulmonary lesions. In one area alveolar septa and interstitium showed dense lymphocytic infiltration (fig. 133). These infiltrates contained many atypical cells of the same appearance as in the liver. Such atypical cells were abundant in the alveoli (in this area, not elsewhere in the lungs) together with obvious alveolar macrophages with erythrophagocytosis. This patient had not received radiotherapy or cytotoxic substances. The alveolar macrophages may sometimes be very atypical after treatment, but here the cells were obviously identical with those in the lymphocyte infiltrates. Mitotic figures were seen also among cells in the alveoli. - The changes in this case would probably have been regarded by most pathologists as malignant histiocytosis or histiocytic medullary reticulosis. One could, however, see morphologic transitional forms between the immunoblast-like and the histiocyte-like cells.

In 136/58 the lymph nodes, liver and spleen showed a very bizarre proliferation in the form of large tumorous nodules. The cells were similar to those in the preceding case (fig. 135). They showed complex tortuosity of the nuclei and abundant cytoplasm with vacuoles and often spider-like inclusions in vacuoles. Between these cells there were very large amounts of histiocytes with obvious phagocytosis of both erythrocytes and lymphocytes. Both types of cells showed mitosis and the cytoplasm was of similar appearance. But no bizarre cells with obvious phagocytosis were seen. Some lymph nodes and other lymphatic infiltrates showed an ordinary CLL-picture without histiocytic infiltration and it was obvious that the bizarre cells and the phagocytising histiocytes were topographically related to each other. The treatment of this patient is unknown because his hospital records were incomplete. It might be added that HL-tissue was everywhere related to the lymphatic infiltrates, never with myeloma foci, which the patient had in the skeleton. - Also this case would probably have been regarded by most pathologists as malignant histiocytosis or histiocytic medullary reticulosis.

In 961/61 the patient had HL-changes in the lymph nodes, paranasal sinuses and base of the skull. In this case the tumour was clearly fibroplastic (figs. 138, 139). The tumour-cells were very polymorphous and grew fascicularly, in some areas almost like fibrosarcoma with abundant reticulin and collagen between the tumour

cells (figs. 140, 141). Between these fascicles of connective tissue-like tumour cells were free cells, also anaplastic and with vacuolated cytoplasm, but without phagocytosis, and cells with plasmocytoid features (fig. 142). This patient had received short terminal radiotherapy of the cervical lymph nodes, but also non-irradiated lymph node sites showed the same picture. These changes would presumably have been regarded by most pathologists as malignant histiocytosis or possibly even malignant fibrous histiocytoma.

HL-CHANGES IN OTHER GROUPS. The HL-changes are summarised in table 15.

	Total number in series	Develo- ped HL	%
LLD-1	94	12	13
LLD-2/Bone marrow group 2	12	1	8
Bone marrow group 1-3	4	1	25
LLD-3	9	5	56
LLD-4	15	1	7
LLN	13	6	46
Macroglobulinemia *	9	2	22

* incl. non-Malmö-cases

Table 15. HL in lymphocytic lymphomas in total material.

The bone marrow group 2-case with HL was 655/63. The patient, a man aged 81 at death, had sought advice because of generalised enlargement of the lymph nodes which he had had for 2 years. The liver and the spleen were moderately enlarged. WBC 43,500 with 98 % lymphocytic cells and immature ++. He had some very large atypical cells with several nucleoli and irregular nuclei (fig. 164). The bone marrow contained 50 % lymphocytic cells with immature +++ (fig. 163). Electrophoresis showed immunoglobulin 0.48 gram/100 ml and a monoclonal component of 0.60 gram/100 ml of IgM-type. The urine contained an Ig μ -component. The patient was treated with chlorambucil, which was withdrawn after 12 days because of nausea and was replaced by corticosteroids. He survived 14 months and was troubled by intermittent attacks of fever. WBC varied between 13,000 and 92,000 without any clear tendency. The hemoglobin concentration fell successively, the concentration

of the monoclonal component remained unchanged.

Necropsy showed diffuse myelofibrosis with lymphoid infiltration (fig. 165). The spleen was shrunken after a subtotal infarction, the liver was of normal size, but showed fibrosing lymphatic infiltrates in the portal tracts. The lymph nodes were enlarged and showed stratified fibrous foci, where the periphery sometimes consisted of polymorphous plasma cell-like forms. A markedly enlarged axillary lymph node showed a central multi-lobulated HL-focus (fig. 167). It was made up of a mixture of IF-cells, small lymphocytes and bizarre multinucleated cells, in some respects resembling Reed-Sternberg cells. They had very basophilic cytoplasm. No fibrosis in this focus (figs. 166, 168 - 170).

The stratified hyaline foci in the lymph nodes might perhaps have been "healed" HL of the same type as the highly cellular lesions in the axillary lymph node. It should be observed that the patient had not received radiotherapy or aggressive cytostatic therapy, which might have resulted in extensive tissue destruction. Both clinically and morphologically the condition resembled Hodgkin's disease, but the cells fitted in best with the group "pleomorphic HL" (see 55).

Group 1-3 (see chapter 5). One of the 4 patients in this group developed HL (437/67). The leukemia had been diagnosed in this man 246 months before death, but he had had hardly any symptoms and received no treatment for about 20 years. Seven months before death he began to have swallowing difficulties because of a tumour of the mesopharynx. Biopsy showed HL in the form of densely packed, large, round cells with prominent nucleoli (fig. 75). The cells contained PAS-positive, hyaline inclusions. Such inclusions were seen as Russel-body-like structures in smears from the cervical lymph nodes, where the cells were very polymorphous with complex tortuosity of the nuclear contour (fig. 74). The WBC at the time of diagnosis of HL was 175,000. Deltisone and radiotherapy were given, but the patient died from increased intracranial pressure. Necropsy showed a large tumour of the throat which had broken through the base of the skull and into the cerebellum. HL was found also in the cervical lymph nodes and in the supraclavicular fossa as well as in the retroperitoneum. The bone marrow and liver showed lymphocytic infiltration without HL as did other lymph nodes. The spleen showed clear IF suggesting that in this case the picture of a biopsy specimen might have been of type LLD-1, despite the atypical cytology. In some areas, the tumour cells closely resembled plasma cells and were full of Russel-body-like formations, which pushed the nucleus to the periphery (fig. 79). The lymphocytes never contained such inclusions.

This patient had an M-component (IgGK) already at the first electrophoretic examination about 5 years before death. Repeated control examination showed unchanged concentration (0.30 - 0.40 gram/100 ml).

A further patient (913/72) in this group had an M-component. It was observed at the first examination 30 months before death. It had increased slightly in concentration by the time of the last examination 1 month before death. The patient died from myocardial infarction 49 months after the diagnosis without having had any noteworthy symptoms of the leukemia. The necropsy specimen contained some lymph nodes with undoubted IF.

LLD-3. Of the 9 patients, 5 developed HL.

1120/60 survived only 7 months after the diagnosis. At the time of the diagnosis the WBC was 6,200 with 68 % lymphocytes with occasional atypical ones (fig. 36). The bone marrow showed moderately dense, diffuse infiltration of partly atypical lymphocytes without evident immaturity (fig. 35), thus a picture best compatible with LLD-3. This patient was given radiotherapy towards the peripheral nodes, which were generally enlarged. The WBC increased, but did not reach leukemic levels, but the percentage of lymphocytes exceeded 90. Afterwards the WBC fell as did the percentage of lymphocytes after treatment with chlorambucil. During the last 2 months the patient became rapidly worse with frequent fever peaks and intractable growth of the lymph nodes. At the time of diagnosis the biopsy specimen of the lymph node showed LLD-3 (fig. 37). At necropsy HL-lesions were predominant in the lymph nodes of the mediastinum and retroperitoneum (fig. 38), while peripheral lymph nodes showed LLD-3. The bone marrow exhibited the same picture as at the time of the diagnosis (fig. 34).

This patient had an M-component (IgGL) which increased in concentration during 6 months in the following way: 0.57 - 0.97 - 1.04 - 1.41 gram/100 ml.

855/67, a man, aged 63 at death, survived 137 months after the diagnosis. He had then already a history of many years with enlargement of the peripheral lymph nodes, chills, diarrhoea, splenomegaly and purpura of hyperglobulinemic type. Liver biopsy 5 years before the diagnosis showed portal lymphocytic infiltration (specimen no longer available). He had a positive test for antinuclear factors and a massive diffuse increase in immunoglobulins, 5.6 gram/100 ml. Examination of the bone marrow on 8 occasions during the disease showed massive plasmocytosis, but never lymphoma infiltrates. Never were the blood values leukemic, but occasionally there were up to 60 % "atypical lymphocytes" in the peripheral blood. Autoimmune disease was suspected. The diagnosis of lymphoma was obtained at exstirpation of the spleen and biopsy of a retroperitoneal lymph node. Splenectomy improved the strange clinical picture, and for some years after a short course of TEM-treatment the patient felt much better. After 3 years the patient's general condition became worse again and severe anemia developed. He was given chlorambucil and improved considerably. Six years before death an M-component of IgM-type appeared. It reached a concentration of 2.45 gram/100 ml. Corticosteroid treatment was started and the patient improved clinically and the M-component disappeared. He began to drink heavily, however, and deteriorated rapidly. During the last 6 months of life, the patient had continuous fever alternating with temperature peaks of above 40°C with severe chills. Massive neutrophilia, 30 - 40,000 WBC. The patient died in a state of shock.

Necropsy showed intestinal bleeding. The liver was cirrhotic. The liver and retroperitoneal lymph nodes showed HL (figs. 173, 174) and the HL-tissue necrotising arteritis and massive granulocyte infiltration (fig. 175). HL was of characteristic immunoblastic type. HL-foci were always surrounded by lymphocytic infiltrates.

290/70, a woman, aged 84 at death, had as a first symptom of her disease bleeding from a polypous HL in the nose (fig. 177). The enlarged cervical lymph nodes were punctured and showed a dominance of large, round tumour cells with very

basophilic, abundant cytoplasm and often excentric nuclei (fig. 178). Other palpable lymph node sites contained only nodes of normal size, but the liver and the spleen were considerably enlarged. The WBC and percentage of lymphocytes were normal. Marked polyclonal increase of immunoglobulins. No M-component. The patient was treated with irradiation of the neck and was in a good condition for some time, but later had gastrointestinal bleeding which proved fatal 8 months after the diagnosis. Never lymphocytosis of the blood. Necropsy showed HL of the lymph nodes in the supraclavicular fossa and retroperitoneum as well as an ulcerated tumour in the stomach, which was the origin of the fatal haemorrhage. Centrally the tumour showed HL and, in the periphery, LL. Other lymph node sites showed LLD-3, as did the liver, spleen and bone marrow (fig. 176).

This patient had probably had asymptomatic LLD-3 for some time. The enlargement of the spleen and liver found already at the time of the diagnosis was due, as judged from the necropsy findings, to LLD and not to HL. The symptoms, however, did not appear before HL-transformation in the air-passages. Literature cases of CLL appearing after HL (see 73) are probably cases of this type, where HL developed from aleukemic LLD-3 and where the lymphocytic part did not become leukemic until after HL-transformation. If the primary HL-manifestations are successfully treated, LLD may persist and give rise to a leukemic blood picture later.

705/70 was a man, aged 63 at death. Lymphoma was diagnosed 27 months before death, but he had a previous 5-year history of asymptomatic enlargement of the cervical lymph nodes. WBC at the time of diagnosis 4,000, 72 % lymphocytes. The patient was treated with Prednisone and chlorambucil and the WBC fell, first to subnormal level, afterwards it rose again and reached 13,700 with 97 % lymphocytes. Four months before death the patient deteriorated rapidly with anemia, loss of body weight and shortness of breath as well as constant fever. Roentgen examination showed a rapidly growing mediastinal tumour. Electrophoresis of the urine showed an M-component in the form of kappa-chains in low concentration. This examination had not been done before. The serum immunoglobulin had fallen to normal level after previously having been increased. The patient died from hyperpyrexia.

Necropsy showed HL in the mandarine-sized mediastinal lymphomas, LLD in other lymph nodes, liver, spleen and bone marrow. HL was histologically of immunoblastic type:

1140/71 was a 58 year old woman, who survived for only 7 months after the diagnosis. From the beginning she had generalised enlargement of the lymph nodes. WBC 4,600, lymphocytes 42 %, slight bone marrow infiltration (fig. 29). The lymph nodes showed many immature cells similar to IF-cells, but more irregular in shape and size. They were somewhat unevenly distributed in loose collections, which could have some slight similarity to IF. In spite of treatment with Velbe and irradiation the patient deteriorated very rapidly. Post mortem revealed in most sites diffuse lymphocytic lymphoma. The mediastinal, supraclavicular and retroperitoneal nodes, and the liver and spleen, contained foci of a bizarre-celled tumour, most closely resembling Hodgkin's disease (figs. 31, 32). The foci had a slightly granulomatous appearance and contained many multinucleated cells resembling

Reed-Sternberg cells. Plasma cells and eosinophilic leukocytes were sparse.

In LLD-3, then, 5 of 9 developed HL or Hodgkin's disease. Three of those 5 had monoclonal immunoglobulin components. Another patient (220/72) in this group also had a small monoclonal component in the form of light chains in the urine. This patient died from non-lymphoma disease 40 months after the diagnosis, 15 months after the detection of the monoclonal component.

LLD-4. One patient in this group (451/61) developed HL. This patient had both clinically and microscopically some similarities to LLD-3.

451/61 was a man, aged 60 at death, who had had leukemic disease for 27 months. He had constantly had diffusely increased immunoglobulin without M-component. He was treated from the beginning with chlorambucil and Deltisone. The spleen caused mechanical symptoms and hyperhemolysis and was removed 1 year after the diagnosis. It weighed 2,800 g and showed massive lymphatic infiltration of the red pulp and expanded follicles with cells of LLD-4-type. The lymph nodes in the spleen hilus exhibited massive plasma cell infiltration in the tumour tissue (but the spleen did not). The increased immunoglobulin level was not affected by splenectomy, but the hyperhemolysis disappeared. The patient was afterwards in a good condition until 4 months before death, when the liver and the lymph nodes increased rapidly in size and the patient died after rapid deterioration despite irradiation of several lymph node sites. Terminally the WBC was about 40,000 with no tendency to fall or rise.

Necropsy showed HL in all the lymph nodes, tonsils, liver, retroperitoneal soft tissues etc. There was insignificant residual lymphatic infiltration except in the bone marrow, where HL was seen as small foci in diffuse lymphocytic infiltrates. The liver (3,400 g) showed a picture that could not be distinguished from that of the corresponding changes in the CLL-cases, a portal lymphocytic infiltration with central foci of HL. HL was histologically of the immunoblastic type with large, round cells with abundant cytoplasm and prominent nucleoli, but with coarse chromatin structure.

LLN. Almost 50 % of the patients in this group developed HL (figs. 179, 180). These cases will not be further dwelt upon here. As a general rule it can be said that the HL-tissue in these cases was more polymorphous than in the above-mentioned groups. In most of the cases extra-lymphatic HL-tumours were found in many sites.

RELATION HL - MONOCLONAL IMMUNOGLOBULIN COMPONENTS. The monoclonal immunoglobulin components in some of the groups and their relation to HL are given in table 16. In LLD-4 and LLN only 1 patient with monoclonal immunoglobulin component was seen in each group and the figures are not included for those types. In the groups included in table 16, 45 % of the patients with monoclonal components developed HL, compared with 12 % of those without monoclonal component, *i.e.*, HL was more than 3 times as common in patients with a monoclonal component.

If IF-n be regarded as potentially HL, it will mean that all together 78 % of the patients with monoclonal components in the material developed HL or potential HL (14/18). Further, it should be observed that the monoclonal components

Diagnosis	Number of patients examined with electrophoresis	With monoclonal immunoglobulin components		Without monoclonal immunoglobulin components	
		Number	HL	HL	IF-n
LLD-1	77*	11	3/11	9/66	18/66
LLD-2/Group 2	11	1	1/1	0/10	-
LLD-3	8	4	3/4	1/4	-
Group 1-3	4	2	1/2	0/2	-
Total	100	18	8/18	10/82	

* One excluded because of myeloma with monoclonal component. This patient also developed HL.

Table 16. Relation between monoclonal immunoglobulin components and HL in some lymphoma group.

appeared to occur most often late in the course of the disease. In many of the HL-cases there was no electrophoretic control examination during the last year (as, of course, in the other cases). In about 25 % of the cases with HL or IF-n but without known monoclonal component no electrophoresis was performed during the last year of life.

The findings lend strong support to the assumption that HL is a neoplasm of the immunoglobulin producing cell series, at any rate the HL that develops in the final phase of the above-mentioned groups of lymphocytic lymphoma. It has not been proved by these observations that the monoclonal components really are produced by the tumour cells, but they probably are.

Chapter 10

SPECIAL HISTOLOGIC AND ELECTRON MICROSCOPIC STUDIES

It has been claimed (37) that positive staining with periodic acid Schiff (PAS) in lymphocytic tumour cells excludes the diagnosis CLL, even if it is only a question of an occasional cell. The PAS-positivity may be diffuse in the cytoplasm or it may be seen as globules in the cytoplasm, resembling Russel bodies in plasma cells (fig. 161). Also, it may be seen as globular nuclear inclusions (fig. 162), resembling so-called Dutcher bodies in macroglobulinemia (see chapter 1). Such PAS-positivity is said to be a sign of production or storage of immunoglobulins, which, according to Lennert et al. (37), excludes the diagnosis CLL by definition. This is obviously a semantic question. I will return to this point in chapter 12.

All the lymph node biopsy specimens from groups LLD-1, -2 and -3 from which tissue was available were stained with PAS. The results are given in table 17 and compared to the immunoglobulin recordings of the case.

PAS-positivity of the above-mentioned types does not appear to have any close connection to monoclonal immunoglobulin components in plasma. This does not exclude that the PAS-positivity represents storage of immunoglobulins intracellularly, but this aspect was not studied in the present material.

The PAS-positive cells were not numerous in any case of LLD-1. The classification as positive or negative was made after search in one section, but case 258/68 (registered as positive in table 17) was negative in the first section. In order to check the reliability of a classification based on PAS-staining, 5 sections were made of this case and searched in oil immersion magnification. In the 3rd section one cell with a typical intranuclear globule was found (fig. 162) and one cell with typical intracytoplasmatic globules (fig. 161). It is thus evident that a vast amount of cells may have to be examined before a positive example is found. When should a specimen be declared as negative? It appears little useful to attempt a histologic classification based on this single criterion. Also, similar hyaline globules staining negatively with PAS may be seen in LLD-1 (personal observations). PAS-staining is not always reliable when performed on necropsy specimens. It was therefore not judged as useful to perform the reaction on all the necropsy cases.

Representative tissue from all of the above mentioned HL-cases in the groups LLD-1, LLD-2/bone marrow group 2, bone marrow group 1-3 and LLD-3, were stained with the methods described below. When biopsy specimens were available they were used, otherwise necropsy specimens. In one case with IF-n a node was also stained and biopsy nodes of the 2 cases of LLD-2. Further the spleen with HL from the macroglobulinemia case 1224/70 was stained.

Giemsa

Silver impregnation for reticulin

Per-iodic acid Schiff (PAS)

Pyronin and methyl green

DIAGNOSIS NUMBER OF CASES WITH MATERIAL AVAILABLE FOR PAS-STAINING	PAS-POSITIVE LYMPHOCYTIC CELLS PRESENT	PAS-POSITIVE CELLS WITHOUT MONOCLONAL IMMUNOGLOBU- LIN COMPONENT		MONOCLONAL IMMUNOGLOBULIN COMPONENTS	
				WITH PAS- POSITIVE CELLS	WITHOUT PAS- POSITIVE CELLS
LLD-1 12	5	3		2 ^x	1
LLD-2 2	0				
LLD-3 7	3	1 ^{xx}		2	

^xONE OF THE PATIENTS HAD MYELOMA

^{xx}THIS PATIENT DEVELOPED A MONOCLONAL COMPONENT 5 YEARS LATER

Table 17. Relation of PAS-positive cells and monoclonal immunoglobulin components.

Prussian blue

van Gieson

Ladewig

Naphthol-AS-D chloracetate esterase

The last mentioned staining method was done according to (34), Ladewig according to (32). All others, according to the routine methods of the laboratory.

This part of the investigation was not very rewarding.

GIEMSA. Staining of necropsy specimens is unreliable. In the biopsy specimens, IF-1-cells can be shown to have intensely basophilic cytoplasm and darkly staining nucleoli (fig. 182). IF-2-cells have a greyish staining of the cytoplasm and nucleoli (fig. 182). The biopsy specimens with HL showed a very variable basophilia of the tumour cells in the individual cases but a large percentage was always very basophilic. Examination of smears with May-Grünwald-Giemsa staining is preferable if the different cell types can be identified in the specimens for cytological study.

Giemsa-stained sections were used for an evaluation of mast cells. Such cells were not estimated to be more numerous in cases with monoclonal immunoglobulin components than in other cases.

PYRONIN AND METHYL GREEN. Also this stain is less reliable when performed on necropsy specimens, at least when the tissue has been fixed in formalin. The pyroninophilia was parallel with basophilia in Giemsa and the staining is not very meaningful.

NAPHTHOL-ASD-CHLORACETATE ESTERASE. Mast cells and polymorphonuclear leukocytes in the sections are practical controls, as they stain positively.

The HL-cells were invariably negative. This argues strongly against confusion with myeloid leukemia or extra-medullary hematopoiesis. In the biopsy specimens some reactive histiocytes always showed some slight reaction; the tumour cells, never. IF-cells and prolymphocytes were always negative.

LADEWIG. After Lennert's recommendation this staining was done which is said to allow differentiation of immunoglobulin containing inclusions of cells in such a way that IgM-containing inclusions stain blue-grey and IgA or G containing inclusions red. Three cases showed hyaline inclusions in abundance in some cells, namely the spleen in the macroglobulinemia case (1224/70), where the inclusions stained red, and 437/67 (monoclonal component of IgG-type), where the inclusions stained red in some cells, blue in others, and in still others both red and blue (fig.80). This varying stainability was not affected by variation in the technique by changing the staining times or concentration of the stains. Case 31/67 (monoclonal component of IgM-type) had numerous plasma cells with PAS-positive inclusions in the foci of Hodgkin's disease. They stained bluish in Ladewig. The result was thus not in agreement with what was expected and is not discussed further.

PRUSSIAN BLUE. Practically all tissues contained some stainable iron in reactive histiocytes. The spleen in the case of macroglobulinemia contained abundant iron but never in the tumour cells. Nor was stainable iron found in any other case in tumour cells, not even in the apparently histiocytic cells in 42/65, 961/61 or 136/58. But all of these specimens had been obtained at necropsy.

SILVER IMPREGNATION FOR RETICULUM FIBERS. IF and IF-n had no characteristic reticulum pattern nor had LLD-2. All the HL-cases showed some reticulum fibers, but characteristic relation to tumour cells in only 2 cases (42/65 and 961/61).

42/65 had abundant reticulum associated with the proliferation of tumour cells in the sinus (fig. 131).

961/61 showed a fascicular growth of tumour, where the pattern of the cells was closely followed by a dense fibrillar network with both reticulin and van Gieson-positive collagen (fig. 139).

The HL of case 655/63 (LLD-2) contained abundant reticulin as well as collagen. The fibers were coarse and PAS-positive. The hyaline foci in 655/63 were strongly PAS-positive (but negative in stains for amyloid).

The HL in 829/69 showed at electron microscopy abundant reticulin-like material, (fig. 160), which could not be demonstrated light microscopically by silver impregnation.

Silver impregnation is often meaningless because the fibers are seen in PAS and when there is much reticulum, the cells have an arrangement showing this already on routine-staining.

PAS. Sections of necropsy material stained with PAS should be judged with caution. Practically all the cases showed diffuse staining in single reactive histiocytes and also in some tumour cells, especially those that appeared necrobiotic. Three cases showed PAS-positive globules in many cells.

1224/70 (macroglobulinemia). The HL in the spleen showed many cells with large, hyaline inclusions. In some of them the nucleus had been pushed to the periphery. They were strongly PAS-positive (same inclusions as those that stained red in Ladewig).

Biopsy of the throat tumour (HL) in 437/67 showed abundant small PAS-positive globules in many tumour cells (fig. 79). Necropsy specimens showed more advanced changes of this type. The globules resembled Russel bodies.

In foci of Hodgkin's disease of case 31/67 there were many cells with the morphology of ordinary plasma cells, which contained densely packed, small PAS-positive globules.

In 1224/70 the inclusions were so large as to deform the nucleus and it is therefore difficult to say whether they really were situated in HL-cells. Also surrounding infiltrates showed such globules but fewer than in the HL-focus.

The cells with PAS-positive globules in 31/67 had a characteristic plasma cell morphology. It is not unusual to find PAS-positive globules in reactive plasma cells in inflammatory conditions. A connection with the tumour proliferation cannot be regarded as proved.

437/67 showed Russel body-like formations which were undoubtedly situated within the tumour cells. But this does not definitely prove that the cells are producers of immunoglobulin. One can find PAS-positive, hyaline inclusions also in reticular cells in benign hyperplasia of the lymph nodes.

These histologic studies are thus non-conclusive in the evaluation of the nature of the cells. To locate the site of production of the M-component, immuno-histochemical studies would have been preferable. The difficulties encountered in fixed material are obvious but can possibly be overcome. Investigation of this point are in progress.

ELECTRON MICROSCOPY. In none of the cases had material been ideally fixed for electron microscopy, but some information can be obtained from material fixed in formalin, if this fixation has been good. All the specimens studied were obtained from paraffin blocks. The tissue specimens were originally fixed in 10 % neutral formalin for a varying length of time. They were afterwards prepared for light microscopy according to routine methods and embedded in paraffin. With the light microscopic section as a guide an interesting part of the block was cut out. It was deparaffinised in xylene and passed through a series of ethanol dilutions to water and postfixed in 1 % osmium tetroxide in phosphate buffer at pH 7.3. The specimens were dehydrated in a graded ethanol series and treated "en bloc" with 1 % phosphotungstic acid and afterwards passed through styrene to Vestopal. Sections (1 μ) were cut and stained with toluidine blue. For electron microscopy the ultrathin sections were stained with uranyl acetate and lead citrate. Mounting on single-hole, formvar film-coated grids was found useful to survey large areas.

The description of IF is based on 3 cases, one of which is not otherwise included in the present material. The patient was a man, aged 62, with recently diagnosed CLL; WBC 500,000 with immature ++ (also in the bone marrow) but predominantly small and mature lymphocytes. Low immunoglobulin level. No M-component. No PAS-positive inclusions. The biopsied inguinal lymph node was the size of a walnut and showed IF +++ (fig. 181). This specimen was best preserved and, unless otherwise stated, the illustrations originate from it, but the other cases exhibited similar changes. The case will be referred to as 2-219. The other two specimens were lymph nodes from 829/69 and 669/73, which were also examined in HL-phase in respectively biopsy specimens of a lymph node and of the gingiva. Further, lymph node biopsy specimens from 663/58 and 671/66 (LLD-2) and of the pharynx (HL) of 437/67 (group 1-3) were examined.

CLL. The larger the lymph node, the closer the cells were crowded, which is perhaps natural owing to the tight capsule of the lymph node.

In all the cases the mature lymphocytes were preponderantly round, but occasional nuclei with deep clefts or with crenated contour were always seen. Many of the mature lymphocytes contained a small nucleolus, often annular, and often adjacent to a mass of condensed chromatin. The heterochromatin was mainly peripheral, but blocks of heterochromatin were always seen also more centrally within the nucleus. The cytoplasm contained free ribosomes, polyribosomes and sometimes single short strands of granular endoplasmic reticulum (GER) as well as mitochondria and a Golgi complex. The outline of the cells was most often smooth, but interdigitation was sometimes seen.

IF. IF were characterised by extremely complex surface relations between the cells, which had long interdigitating processes and no free intercellular space was apparent (figs. 183, 189). In a single plane of section it was often difficult or im-

possible to decide from which cell a given process extended, but after tedious examination it was possible to form an opinion of the relation of the organelles of a process to a certain type of nucleus. The cell nuclei in IF were sparsely distributed which probably explains why IF appear as pale areas in low magnification in the light microscope. This sparseness was due to the large amount of interdigitating processes and the more abundant cytoplasm in the IF cells than in mature lymphocytes in the surroundings. In sections from one single plane it was often impossible to classify every cell electron microscopically because the sections are so thin that they can contain only a limited number of cellular elements. The description is based to a certain extent on serial sections, and it is difficult to illustrate all the characteristics of the various types of cells in a few reproductions. After exacting work with these structures I felt that all forms of cells in IF are genetically related and that there are at any rate such similarities between them that for the reasons given above it is not possible to classify every single cell in a single plane of section. Sometimes cells were seen which appeared to have features intermediate between those of the main types. It cannot be excluded that such intermediate forms of cells really exist and are examples of different developmental stages, but it is more likely that the phenomenon was generally due to sectional effects. A tangentially sectioned immature cell may be difficult to distinguish from a mature lymphocyte because a tangential section of the nucleus leaves the impression of greater condensation of the chromatin and because the types of cells resemble each other in cytoplasmic structure. But if the section passed through the nucleolus it was usually possible to classify the cell.

The following main types of cells could be distinguished:

1. Mature lymphocytes, which did not differ from those in the surrounding parenchyma.

2. Prolymphocytes. The chromatin condensation was not so marked as in the mature lymphocytes and the nucleolus was more prominent and had a more marked nucleolonema. The cytoplasmic structures, however, were very similar to those of 1. The prolymphocytes were smoother in outline than the following types of cells, but single interdigitations were seen along the outline of every cell.

3. IF-1 cells. These cells were uncommon and could be detected only after a search in light microscopic sections, and even then they were sometimes difficult to find. The diameter of the nucleus was 3-4 times that of the nucleus of mature lymphocytes (fig. 188). IF-1 cells were often situated close to a small vessel. The nucleus was never quite round and it had not the smooth outline of the IF-2 cell. Several nucleoli without any particular position in the nucleus were always seen. Very small chromatin blocks were observed peripherally, but, on the whole, the chromatin condensation was slight. The cytoplasm had sparse organelles besides polyribosomes, which diffusely filled the cytoplasm. Occasional strands of GER were usually demonstrable as well as single mitochondria and occasionally proto-lysosome-like bodies. The cells were star-shaped with broad processes.

4. IF-2 cells. The diameter of the nucleus was roughly half that of the IF-1 cell (fig. 189). The nucleus had a very smooth outline, but was often slightly indented. A large nucleolus was seen in all these cells, most often in a central position in the

nucleus. It consisted mainly of a complex nucleolonema and the pars amorfa was less prominent. The chromatin condensation was intermediate that of the IF-1 cell and the prolymphocyte. The cytoplasm contained fewer polyribosomes and more GER than the IF-1 cell, but only 1 or a few strands were seen in each sectional plane. Occasionally there were parallel stacks or whorls of GER but it was never dilated (fig. 194). Single cells contained a lamellar ribosome-studded membrane complex of the type seen in leukemic reticuloendotheliosis (hairy cell leukemia, see survey in 28) (fig. 199). The mitochondria were more numerous in the IF-2 cells than in the IF-1 cells.

The IF-2 cells had long processes which were often bifurcated and enclosed another cell process (fig. 189). The longer processes often had bundles of microtubuli and fine filaments (figs. 184, 185) that were characteristically arranged along, and, situated obliquely to, the cell surface and sometimes inserting in desmosomes. Desmosomal connections were also seen between short, intertwining processes of such cells, and between such and the body of other IF-2 cells (figs. 196 - 198) and also prolymphocytes.

Most of the mitotic figures observed were obviously those of IF-2 cells, as judged from cell size and organelles (fig. 194).

Many IF-2 and IF-1 cells of case 2-219 contained bundles of wavy, thread-like formations, which were round or irregular in cross section (figs. 203, 204). No lumina were seen with certainty. They were of uniform thickness and about 17 nm in diameter. They were not related to the endoplasmic reticulum. Sometimes they were seen close to membrane bound bodies containing polymorphous membranous material and electron opaque, structureless material (fig. 203). Similar structures were seen in occasional cells in one of the cases of LLD-2. In some respects the structures resembled paramyxovirus, but it was not possible to characterise them more exactly in this poorly fixed material. No such formations were ever seen within the nuclei. Otherwise no structures were seen that resembled any virus component or other micro-organism. In case 2-219 the mature lymphocytes contained numerous electron opaque bodies, about 0.3 μ in diameter, surrounded by membranes and resembling so-called Gall-bodies. Such bodies were abundant in the IF-2 cells and in prolymphocytes (fig. 193). They were often seen in a small cluster of lysosome-like granules.

In 829/69 the cytoplasm exhibited densities at various points of contact between the processes. Within these areas the intercellular space was bridged by thin, paired spicules (figs. 150, 151).

5. IF (and LLD-2) contained many cells with the following characteristics. The cell is hereinafter referred to as the IF-3 cell, in spite of the fact that some similar cells were seen among the mature lymphocytes outside IF (as also single IF-2 cells and an occasional IF-1 cell were seen).

The size of the nucleus in the IF-3 cell was equal to that of the IF-2 cell, but the nucleus was always elongated (figs. 190, 191). The chromatin structures were similar, but there was a stronger tendency to formation of a thin continuous layer of condensed chromatin under the nuclear membrane. The nucleolus was often smaller. These cells had a polarised cytoplasm and the cell body was elongated,

tapering in direction from the nuclear pole (fig. 190). From the body of the cell extended narrow branches that interlocked with the processes of the other IF-cells and showed desmosomes. These cells were practically always associated with reticulin structures. These structures consisted of collagen-like fibril-bundles embedded in amorphous substance, which was very electron opaque in the method used (fig. 202). Similar fibrils were sometimes seen close to other cells but this may be due to incidental apposition. The cytoplasm of the IF-3 cells was "lighter" than that of the other cells because of the sparseness of polyribosomes. On the other hand, there was a more abundant GER which differed from that of the other cells in that the strands were shorter and coarser (fig. 193). Mitochondria were abundant and the cells always contained bundles of fibrils - more than the IF-2 cells - also in a perinuclear position. Gall-body-like granules of exactly the same appearance as in the IF-2 cells were often demonstrable in case 2-219 (fig. 193). - It was obvious that these cells had features in common with reticulum cells. See also fig. 192 .

6. Macrophage-like cells. These cells were irregularly distributed. The nucleus was characteristically irregular with deep clefts and pockets and the chromatin condensation was slight (fig. 200). Often no nucleoli were seen. The cytoplasm was irregular in shape, often polarised in a way resembling that seen in the IF-3 cells. It contained abundant organelles of various types. Numerous lysosomes were always seen and also phagosomes.

7. Case 2-219 was found to contain a small number of cells differing clearly from all other cells in the IF in that they had an entirely smooth outline and no processes or interdigitation. They had a smooth outlined, slightly ovoid nucleus and a small nucleolus. They were also recognized by their abundant lamellar GER and contained small lysosome-like granules. These cells resembled pro-plasmocytes (fig. 201).

8. All IF contained sparse examples of another type of cell with electron opaque nucleus, often situated close to a vessel, and with long processes with very electron opaque cytoplasm containing abundant GER and crowded monoribosomes and compact bundles of fibrils. The processes were of astonishing length and extremely thin. Owing to their electron opacity they could be readily traced through the section, sometimes along a distance of several hundred microns (fig. 195). The processes were invariably associated with fiber structures. These cells were probably compressed fibroblasts.

9. Occasional cells with the appearance of ordinary interdigitating and dendritic reticular cells were met with. They had small nucleoli or no visible nucleolus in the plane of section. The dendritic cells were connected by desmosomes to other similar cells (figs. 184, 186, 187).

THE VESSELS OF THE IF. IF were rich in small vessels. On the light microscopic level one often had the impression that the IF was centered on a small vessel with a compressed lumen, often filled with a row of lymphocytes, and with a single row of low endothelial cells (fig. 211). The vessel was surrounded by a basal lamina of moderate width. High endothelium postcapillary venules were always seen in LLD-1, but these vessels seemed to be situated outside the small IF, or, often almost in contact with their periphery. Venules of this type were seen within the larger IF,

however, and there did not seem to be any constant and typical topographic relation between the two structures (fig. 205). The narrow central vessel was sometimes seen to lead directly into a high endothelium venule and also those vessels were probably of a venous or capillary character. From the electron microscopic point of view, there was little to differentiate the two types of vessels except their size. The endothelial cells had bundles of fibrils and other organelles which were of a similar character, except that the high endothelial venular cells had more lysosomal granules than the low endothelium of the narrower vessel. In both vessels the basal lamina was split, in the narrow one at least into two lamellae (fig. 212), in the high endothelium venules into many complex lamellae (figs. 205, 206). Between them there was a layer of cytoplasm belonging to pericytic cells. This was often "clear" with few organelles, but occasional bundles of fibrils were always seen, and generally a few profiles of GER, short and coarse, like the reticulum of the IF-3 cells. Typically, pinocytic vesicles in large amounts were seen, where these cells were apposed to the basal lamina (fig. 208). Within the laminar duplications many lymphocytes were seen in the venules (fig. 207). A peculiar phenomenon was sometimes observed, namely a "clearing" of the cytoplasm when the cell passed a gap in the innermost lamella (fig. 209). In some respects, then, the clear cytoplasm resembled that of the pericytes described above, but true pinocytic vesicles were never seen in cells with preserved lymphocytic character. It is here assumed that the lymphocytes pass from the lumen outwards. The other direction is, of course, possible but from what is known of lymphocyte traffic in the nodes generally, it seems more reasonable to imagine passage outwards. The outermost lamina of the wall was thick and contained collagenous fibrils. The parenchymatous aspect had a moth-eaten appearance and many small blebs and gaps were seen, through which lymphocytes were apparently travelling (figs. 205, 208). The vessel was generally surrounded by a sheath of processes from cells with the characteristics of 5 and 8 above. Those with the appearance of 5 were often, but not always, partly invested in a thin duplication of the basal lamina, trailing off into the parenchyma as a reticulum fiber (fig. 212). Except for the pinocytic vesicles, these cells were similar to the pericytes. Sometimes they appeared to be pericytes breaking loose from the wall. In other places the cells of the parenchyma were directly, and very closely, apposed to the wall. It was sometimes possible by serial sectioning to demonstrate desmosomal connections between IF cells of the parenchyma and cells within the laminar duplications of the vessel wall (fig. 208). Those cells appeared to be pericytes. In the light microscope it was sometimes possible to find venules with a large clump of tightly packed lymphocytes in the centre and where the wall seemed to be in a state of dissolution, thus creating the impression that the venules could be transformed into parenchyma by lymphocyte stagnation.

LLD-2. This examination confirmed the morphologic identity of the cells in this process and those of the IF of LLD-1. The prolymphocytes dominated the picture and IF-1-2 and -3 cells also were seen. A minor portion of mature lymphocytes was always found intermingled with the immature cells (figs. 213, 214).

HL. The gingival tumour in 669/73 and the pharyngeal tumour in 437/67 showed many artefacts, probably largely due to mechanical distortion at the time of

biopsy (performed with a small biopptome). The lymph node tumour of case 829/69 was better preserved and is dealt with first.

The cellular picture was polymorphous with considerable variation in size and shape of cells and nuclei (fig. 156). Cells many times larger than lymphocytes dominated. The nuclei were irregular with many invaginations and "pockets" (fig. 157). But also cells with a smooth nuclear contour, and similar to IF-2 cells, were seen (fig. 158). Generally, the nucleoli were multiple and consisted primarily of nucleolonema. The heterochromatin was moderately prominent and usually peripheral. The cytoplasm was abundant and contained large amounts of GER, partly in parallel formations (figs. 158, 160). Many polyribosomes were also present. The GER demonstrated occasional dilated sacks with structureless material. Bundles of thin cytoplasmic fibrils were seen, most often in the cell periphery and situated obliquely or at right angles to the cell surface. There were many groups of glycogen granules, but mitochondria were not numerous. Many cells were surrounded with electron dense material including fibrils, some of which demonstrated collagen-like cross banding. Thus, there was a close similarity of these structures to reticulum fibers (figs. 159, 160). Desmosomes were never seen, and only an occasional lysosome-like body. Mitotic figures were abundant (fig. 159). Many degenerating or dead cells were met with, often phagocytosed in the cytoplasm of histiocytes. The dead tumour cells often contained round intranuclear inclusions (fig. 155) with high electron density. They consisted of granular or structureless material, seemingly detritus.

669/73. The general character of the nuclei was similar to that of the case described above, but the chromatin condensation was less. GER was not so prominent, still some profiles thereof were seen in every cell at the plane of section. An occasional parallel stack was seen, also such containing granular material of moderate density. Peripheral bundles of fibrils similar to those described above were always seen. There were many vacuoles in the cytoplasm but they were probably artefacts. Occasional lymphocytes were seen intermingled with the HL-cells.

437/67. The cells of this tumour seemed to be of a dual character. Most of them had dark, lymphocyte-like nuclei of irregular shape with condensed chromatin, but with large nucleoli (fig. 76). Others had a larger nucleus with few chromatin clumps and a smooth contour. The latter type of cell contained round inclusions in the cytoplasm, probably corresponding to the PAS-positive structures described earlier (fig. 76). They had a reticular substructure of alternating light areas and dark streaks. They were generally not seen within the membranes of the GER. The dark cell type had markedly plasmacytoid features (fig. 77). Parallel formations of GER including granular material of moderate electron opacity were often seen (fig. 78).

The tumours of both of the last-mentioned cases contained many connective tissue fibers of varying thickness. They might be explained as pre-existing stroma of the tissue infiltrated by the tumour cells.

Chapter 11

DISCUSSION OF THE IMMATURE CELLS, IMMATURE FOCI OF THE LYMPH
 NODES, AND MALIGNANT LYMPHOMA OF HISTIOCYTIC TYPE IN CHRONIC
 LYMPHATIC LEUKEMIA

Understanding of the histogenesis and progression of CLL appears to require elucidation of the nature of the immature cells of the IF and other tissues. The 2 most important questions in this connection are:

1. What is the relation between the different types of immature cells, and between the immature cells and the mature lymphocytes, and
2. Is there any relation between the immature cells and the eventual development of HL?

As for question 1, three possibilities might be considered:

- A. Are the immature cells precursors of lymphocytes?
- B. Are the immature cells descendants of lymphocytes, possibly developed via a process analogous to that of immunoblastic transformation?
- C. Are the immature cells and the lymphocytes independent of each other cytogenetically, but occurring with topographic association?

Here the scope of immature cells include prolymphocytes and the other types of immature IF-cells.

A. According to Lennert, the nodes in CLL show pseudofollicular formations of lymphoblasts (36). Those are what I call IF. Lennert calls them proliferation centers. He thus probably regards the immature cells as lymphocyte precursors. There is in my opinion strong evidence in favour of this view. For the immature cells are those of the CLL tissues which show mitotic figures. The mature lymphocytes are presumably generated by mitosis, and even if they survive for a long time, it must be possible to find the mitotic figures in their precursors. The prolymphocytes, which are the dominating cells of the IF, and mature lymphocytes have so many morphologic similarities that it appears reasonable to assume that one type is derived from the other. As the prolymphocytes are the dividing cells, they are reasonably the precursors. An important question in this connection is whether the prolymphocytes are of the same nature in the blood and in all tissues. They are cytologically identical. Although cytologic identity does not necessarily mean functional identity, it seems improbable that a single morphologic type of cell corresponds to stem cells in the bone marrow and transformed lymphocytes in the lymph nodes, for example. The prolymphocytes are also present in the blood, although usually in low percentage, and they can probably migrate between the various tissues. The prolymphocytes do not resemble the cells of so-called lymphoblastic leukemia of childhood, an irrelevant point, as the exact nature of the cells is uncertain in this disease. Thus, the prolymphocytes are, according to this line of thought, lympho-

cyte precursors. This assumption is also corroborated by the findings of IF-n in the largest infiltrates and those organs most heavily infiltrated. IF-n also contain prolymphocytes, though the more immature forms of IF-cells have gained predominance. The large and atypical cells of IF-n are reasonably dystrophic forms of IF-1 or IF-2 or IF-3 cells. It is difficult to find an explanation for IF-n occurring primarily in large infiltrates, unless they are themselves the site of origin of the lymphocytes of which the infiltrate consists. However, little is known of the release kinetics from the tissue infiltrates. A counter-argument to the theory of the immature cells as lymphocyte precursors is that one cannot demonstrate any exact correlation between the WBC in the peripheral blood, on one hand, and, on the other, the extent of IF in the nodes and of immature cells in the marrow. This relation, however, is dependent on the kinetics of cell division, on the release mechanism and on cell death. The lack of correlation might be explained by the assumption that under certain conditions the immature cells proliferate without maturation, and/or that the mature cells are not released to the blood. The latter may well be the case, especially after treatment, when the WBC may be normal or low in spite of heavy tissue infiltration. Cases with a high percentage of immature cells in the marrow seem to have a tendency to reach very high values of the WBC at some point, but they are not constantly at a higher level than other cases, which may be interpreted as variation in the generation kinetics from time to time. A further complication in the evaluation of the relation between tissue immature cells and the level of the WBC is that the prolymphocytes evidently are released into the circulation as such in considerable amounts in some cases, but not in others. LLD-2, which consists mainly of immature cells, may be aleukemic, suggesting that these cells may be strictly tissue-bound in certain circumstances. The cells in question can, however, sometimes pass into the circulation as such and give rise to the hematological picture of prolymphocytic leukemia. There is no sound basis for speculations about the cause of this variation in the behaviour of the immature cells. But the lack of a linear correlation between the WBC and the percentage of tissue immature cells cannot be used as an argument against the lymphocyte precursor theory. Thus, the prolymphocytes probably generate the mature lymphocytes, by division and maturation of one or both the daughter cells. What, then, is the origin of the prolymphocytes? It does not appear probable that they are lymphatic stem cells. The low nuclear/cytoplasmic ratio is not the rule in stem cells, but is more compatible with an intermediate cell in a maturation chain. If they were stem cells, they would probably be more profuse in the marrow than in the nodes. There are similarities to the IF-2 cells, at least electron microscopically, and it appears reasonable that the prolymphocytes are derived from them. See later discussion of electron microscopic findings.

As for alternative B, the cytologic picture of the IF-1 and IF-2 cells suggest that this may be correct. The low nuclear/cytoplasmic ratio is well compatible with a reactive lymphatic cell form. The IF-1 cells certainly are very similar to normal immunoblasts as seen in a viral lymphadenopathy, for example. Isomorphism is an unreliable criterion, however. But there are other factors to which I shall return later, making it reasonable to consider whether IF cells may not also be analogous

to plasma cell precursors.

The high frequency of mitotic figures in the IF-1 cells and IF-2 cells argues against alternative B. What are the daughter cells after mitosis if they are not pro-lymphocytes or mature lymphocytes? If the IF-cells proper always and exclusively divided homoplastically the IF would reasonably expand rapidly because they show no signs of extensive cell death. As the IF-cells proper are practically never seen in the blood, they can not be released from the nodes as such. Large IF are sometimes seen in association with a low percentage of immature cells in the blood. This can be taken as an argument for the mature blood lymphocytes being the products of the mitosis in the IF. No true plasma cells are seen in the nodes of CLL, for which reason the IF-cells cannot disappear by conversion in situ into such.

As for alternative C above, it appears a priori less probable. Why should a common tumour consist of unrelated cell lines in constant topographic relations? The origin of the lymphocytes would be enigmatic as would the slow or absent expansion of the IF in spite of frequent mitosis.

Most evidence available thus suggests that IF are the origin of the circulating lymphocytes. If this is so, why should there be a relation between IF-n and monoclonal immunoglobulin components? IF-n have so many similarities to the IF of biopsy specimens that it appears certain that they are advanced stages thereof. But it appears incompatible with a theory of lymphocyte production in the IF that they show a correlation to monoclonal immunoglobulin components. It seems probable, though unproved, that the components are really produced by the cells of IF-n, or their descendants.

It is theoretically possible to make a compromise between alternatives A and B, namely that the IF-cells are both transformed lymphocytes and precursors of the mature lymphocytes. The latter should thus be B:2 (or occasionally, perhaps T:2) cells originating from pathologic immunoblasts, the IF-cells. The IF-1 cell should then presumably be the immunoblast, the IF-2 cells and prolymphocytes developmental stages towards B:2 cells. The identity of the B:1 cell is enigmatic. It might possibly be a question of retransformation of leukemic cells, thus a circular series of events in the CLL-process, or clonal expansion by transformation of some other lymphocyte giving rise to a leukemic population of non-reactive cells.

It is pointless to construct an exact scheme of kinetics of such a speculative system but the B:1 population would presumably have to be of considerable dimensions to supply the pathologic process on rapid expansion of the B:2 pool, unless the IF-1 cell, once formed, acts as a true stem cell.

Such a theory might explain the apparent contradiction between the IF-cell as lymphocyte precursor and as immunoglobulin producer, if it be supposed that the immunoblast or its daughter cells can secrete immunoglobulins without assuming the morphology of the plasma cell.

As for question 2 it appears on morphological grounds probable that IF, IF-n and HL are different stages of one and the same process. IF and IF-n had the same topography and partly the same cell content. Biopsy material rarely shows changes corresponding to those seen in IF-n, but this may be because the patient survives only a short time after the IF have assumed the more malignant character which

IF-n seems to imply. Moreover, biopsy specimens are rarely obtained from patients who appear to be in the terminal phase. A lymph node biopsy specimen with a picture of both CLL and HL was observed in 1 case (829/69) and there very marked IF were seen with atypia which might correspond to IF-n. IF-n and HL showed transitional forms. In extensive HL, IF-n were not always seen, but all rests of such may have been eliminated by the more rapidly proliferating tissue. All small HL-lesions were surrounded by lymphocytes in such a way as to suggest that they had started in lymphatic infiltrates. HL in the liver always started in the largest lymphatic infiltrates, which were also the site of the most advanced IF-n. HL was seen less often in the bone marrow, as were IF and IF-n. M-components occurred in the same frequency in patients with IF-n and HL, differing markedly from what was seen in cases without such changes, which also suggests a close relation between IF-n and HL.

Thus, there is reason to suspect a relation between IF-cell and HL-cell. In the light microscope IF-cells are strikingly monomorphous. The morphology of the HL-cells might be divided into 3 groups, namely round, basophilic cells of fairly uniform size (immunoblastic type), elongated, fiber-associated, often polymorphous cells, and more bizarre cells, which are often "histiocyte-like" and have abundant cytoplasm. The last-mentioned type occurs to some extent in tumours composed of one of the other two. None of the HL-cases in the series showed exclusively one or the other cell type, all forms occurring in varying proportions in all the cases. These types are probably variants of the same process. The immunoblastic type is obviously morphologically most closely related to the IF-cell. M-components often occur in association with the development of HL. This might be a reaction of some immunoglobulin-producing cell clone to HL. But the HL-cells often have an abundant GER with an organisation resembling that of plasma cells and they sometimes have an accumulation of substances similar to Russel bodies of plasma cells. As demonstrated by Stein et al. (65), HL often contains large amounts of immunoglobulins even in the absence of abnormal components in the plasma. All this suggests that the M-component is a product of the tumour cells. In those cases where the M-component was found long before the appearance of HL, it might be a question of immunoglobulin production in IF or, in other types of lymphoma, from immature cells analogous to IF-cells. If IF- and HL-cells really can secrete immunoglobulins, they should belong to the B-cell system. According to the theory presented earlier, HL should be seen as a block in maturation from immunoblast to B:2-cell. LLD-2/prolymphocytic leukemia might be a block at an intermediate stage.

If the above theories are correct, the terms HL and reticulum cell sarcoma must be inappropriate. There are, however, factors which are difficult to dismiss, and which argue for "histiocytes" or "reticulum cells" having something to do with this condition. First, it should be emphasised that I now mean only HL developing in CLL. Primary HL lies beyond the scope of the present investigation.

Pictures like the HL in case 961/61 suggest fibroplasia of the tumour cells. An abundance of fibers in the tissue is not per se a definite sign that the cells are of connective tissue character. But when, as in this case, there is an organised mode of

growth, where the fibers and cells closely follow each other and the cells closely resemble connective tissue cells, it appears probable that it is a question of tumour cells with fibroplasia. Also 42/65 showed a close structural relation between the tumour cells in the sinus and the fibrillar sinus reticulum. In this case the tumour cells appeared topographically like sinus endothelium and their behaviour also suggested a potential alveolar cell character. The possibility of the tumour cells having a potential reticulum cell nature is dealt with in the discussion of the electron microscopical findings.

An interesting problem is the relation between the clearly phagocytic macrophages and the tumour cells. The former might be a simple reactive phenomenon in association with tumour cell necrosis, for example. Especially in the cases of Hodgkin's disease, however, they were so abundant that one wonders whether there was not some special relation between them. There is no doubt that it was a question of a special topographic relation. The macrophages and Reed-Sternberg cells always appeared in association. It appears probable that the Reed-Sternberg cells in these cases are closely related to HL-cells. Here, a mention should be made of the literature on "Richter's syndrome". As pointed out in the introduction, CLL followed by Hodgkin's disease appears to be at least as common as CLL-HL. Many of the cases of Hodgkin's disease are classified as Hodgkin's sarcoma but, judging from the illustrations, it is often a question of pictures which would equally well or even better fit in with the designation pleomorphic HL. Characteristic lesions of Hodgkin's disease with a granulomatous character and true Reed-Sternberg cells are probably much less common than HL, but it is obvious that they do occur in this connection. I have seen another 2 cases of Hodgkin's disease eventually develop in patients with CLL (cases not part of this investigation. See fig. 120).

The morphologic findings in the studies of the IF are difficult to interpret. Characteristically, IF were distributed evenly and diffusely throughout the node. They had no constant relation to pre-existing structures. The small vessels seen to penetrate them were so constant, however, that it is tempting to imagine some type of functional relation. Lymphocytes were seen to penetrate the wall and it appears that the cells leave the vessel to enter the parenchyma. High endothelium, postcapillary venules were also seen in all the biopsy nodes of CLL with a lively traffic of lymphocytes through their walls. One might imagine that the cells leaving the 2 types of vessels were different types of lymphocytes but they appeared morphologically similar.

The great majority of the mitotic figures of the nodes in CLL were seen in the IF. Occasional mitotic figures were seen outside the IF, but so were occasional immature cells. I do not think that the IF and the mature parts should be regarded as distinctly separate compartments. The IF are rather local condensations of immature cells, especially prolymphocytes. In the bone marrow the immature cells are generally not so focal in their distribution, and are fairly sparse. Assuming that the immature cells are lymphocyte precursors the majority of leukemic cells should presumably be produced in the nodes. On the other hand, the bone marrow as an organ is incomparably larger than the collected mass of the nodes in early CLL, which weighs against this assumption. However, the IF seem to be primarily nodal

structures. They may also be seen in the lymphatic tissue of the spleen and in the bone marrow, but it was my impression that they appeared late in these organs, and were seldom so prominent as in the nodes. But they were often seen in the liver, and therefore can not be a prerequisite of lymphatic organs in a restricted sense. Further, they were occasionally seen in the renal hilar adipose tissue, where lymphatic tissue is not indigenous.

The chief types of IF-cells have clear morphologic similarities. Does this mean that they are genetically related? This is naturally impossible to prove from a fixed tissue section, but it is reasonable to assume that IF-1 cell, IF-2 cell, prolymphocyte and mature lymphocyte are subsequent generations in a process of maturation. Some of the organelles are identical, such as the Gall-body like structures and the thread-like formations. Also, there is a relation in size between the cell types in question agreeing with such a hypothesis. If so, the IF-1 cell is the most immature form of the leukemic lymphocyte. I think it improbable that the direction of development is from the small lymphocyte of the parenchyma to IF-1 cell, primarily because of the ratio between their numbers. IF-1 cells are rather uncommon, IF-2 cells less so. Supposing a high rate of mitosis, the development of an IF-1 cell into prolymphocytes and lymphocytes through IF-2 cells could well be possible. What, then, is the IF-1 cell? The possibility that it is a diseased stem cell cannot be excluded, but I think it more probable that it is an abnormal immunoblast, developed from some immigrant to the node. If so, it could be regarded as an intermediate cell in the disease process and a search should be made for a "pre-IF-1 cell". As speculated earlier, this might be a circulating lymphocyte expanding clonally into the leukemic population. If this hypothesis is correct, it should be possible to find cells intermediate between lymphocytes and IF-1 cells. The latter are so uncommon, however, and the electron microscopic sections are so thin that this may be an extremely difficult task. The cells should probably be found in close proximity to the vessels. Candidates can be found, such as the cell illustrated in fig. 210, but naturally all this is hypothetic and impossible to prove by static morphologic observation. The events within the lymph node vessel walls could well be of interest in lymphatic malignancies.

What about the IF-3 cells, then? They are certainly similar to reticulum cells with their long branching processes with fibrils and desmosomes. They could be mesenchymal stem cells and the precursors of the other IF-cells. But this seems improbable as they have more and higher specialised organelles than the IF-1 cells. Perhaps it can not be excluded that organelles disappear but it is not a promising hypothesis. On the other hand, IF-3 cells resemble IF-2 cells in various respects. The nuclear structure and the nucleolus are similar and they contain structures identical to the Gall-body-like granules of IF-2 cells and lymphocytes. Some of the IF-2 cells have long processes and many of them have desmosomes. All this might be interpreted as signs of a genetic relation between these cells. If there is, it is more reasonable to assume that the IF-3 cells are derived from the IF-2 cells than vice versa, as the IF-3 cells have more and higher developed organelles.

If all this be correct, the following state of affairs should prevail: an immigrant to the node transforms into an immunoblast (IF-1 cell) within or close to the

vessel wall. This cell multiplies by mitosis into IF-2 cells, thus creating the IF proper. The IF-2 cell is a lymphocyte precursor, but may also be a reticulum cell precursor. All the IF-cells are descendants from the IF-1 cell. When HL develops from the IF-cells, it may therefore have some characteristics of "reticulum cell sarcoma". Further, the IF-cells could well be immunoglobulin producers if they are transformed B lymphocytes. The rare cells found in one case and illustrated in fig. 201 might be a remnant of plasmocytic differentiation, generally almost totally absent. This could explain the monoclonal immunoglobulin component in cases with prominent IF-n and HL.

This theory thus infers that the pathological, transformed cell (IF-1 cell) should have several developmental possibilities, to mature lymphocytes via IF-2 cells and prolymphocytes, to tissue bound cellular elements, "reticulum cells", and to immunoglobulin secreting cells. The latter may possibly in this special pathological situation be morphologically very similar to IF-2 cells. All this is highly speculative, and it appears useless to theorise about why the descendants of the IF-1 cells should sometimes choose one pathway, sometimes another one. The lymphocytic differentiation should be the most "benign" one, while the others appear to imply a poor prognosis.

It may be difficult to accept that reticulum cells are descendants of lymphocytic cells. The opposite is often held to be the case. But reticulum cells are a heterogeneous group and in some situations in adult life they must presumably be re-created from wandering cells. In some respects the IF-3 cells resemble the dendritic reticulum cells of germinal centers. In inflammatory reactions germinal centers may develop almost anywhere and in places where lymphatic tissue is not indigenous the reticulum cells thereof might well be derived from blood-borne precursors. The IF-3 cells can certainly not be only the diluted rest of the original lymph node reticulum cells in the large nodes of advanced CLL. However, evident IF-3 cells are much fewer than IF-2 cells. It is meaningless to construct an exact scheme of differentiation in this hypothetical model, but if it is somewhat realistic, the IF-3 pathway must be much less frequent than the pathway of lymphocyte differentiation. What is the ultimate fate of the IF-3 cells? It seems improbable that they are constant throughout the disease. Once formed, they probably persist for some time as IF-3 cells and then disappear, either through death or by transformation into something else. Otherwise the IF should probably expand more than they really do. It is tempting to speculate that they are transformed into macrophage-like cells. There are some morphologic similarities, and this might explain the morphologic "histiocytic" tendency observed in some of the HL-cases. There is no doubt that the IF-3 cells are associated with reticulum fibers more often than other cells of the IF. This may not prove that they produce these fibers, but it could explain the close association between connective tissue fibers and the cells of some of the HL-cases. No desmosomes were observed in the HL-cases examined. This does not exclude a connection between IF-cells and HL-cells. A poorly differentiated spinocellular carcinoma also may lose the capacity of desmosome formation.

Most studies of HL do not support a histiocytic origin of these tumours, but rather suggest an immunoblastic nature. Some cases have, however, demonstrated high activity of enzymes such as acid phosphatase and esterases, generally thought to belong to histiocytes and macrophages and also phagocytosis (see 17, 22).

Microscopically indistinguishable tumours can be thought either to be derived from different cell types with final similar histology, or to have identical histogenesis with differentiated biological function. The latter alternative might explain that morphologically identical tumours sometimes have immunoblastic characteristics but occasionally have histiocytic activity.

As long as the transformed cells are capable of giving rise to differentiated cells, the conditions of CLL prevail. It is impossible to know what instigates the transformation of the presumed B-1 cell. It may be an internal abnormality and not an external agent. The leukemic B-2 cell population should be memory cells but they may have a "nonsense" memory without immunological function, just as the M-component could be a "nonsense" antibody. If the capacity of lymphocyte differentiation is lost, HL might develop, and the HL cells could then be the IF-1 cells in "malignant degeneration", but possibly with some preserved tendency to histiocytic and/or plasmacytic differentiation.

The histologic picture of LLD-3 obviously has similarities to that of LLD-1. The cells, however, are more atypical and no IF are seen. As LLD-3 in an early stage generally appears to be non-leukemic, this sounds reasonable, because IF predominantly consist of prolymphocytes, which, according to what was previously said, probably are precursors of the leukemic lymphocytes. When HL develops in LLD-3, the type of cell is very similar to the HL in LLD-1. IF-n were not seen in cases of LLD-3 and the transformation to HL microscopically appeared to be more diffuse, although, from a gross morphologic point of view, focal in character. Apart from the case resembling Hodgkin's disease, the HL in LLD-3 was of predominantly immunoblastic type. This argues for a close connection between LLD-1 and LLD-3, and also some cases from a cytological point of view appeared to be intermediate. They are probably closely connected diseases, but nevertheless the vast majority of cases can be classified as one or the other. Possibly they should be seen as clustering points on a continuous spectrum. But LLD-3 also had similarities to LLD-4 and one case was somewhat dubious as to classification LLD-3 or LLD-4. LLD-4, on the other hand, appeared to be a diffuse variant of LLN. It would thus appear that all the lymphocytic (and also some histiocytic) malignant lymphomas are closely connected conditions. A case starting as a typical example of one type of lymphocytic lymphoma seldom appears to transform into another type of lymphocytic lymphoma (except for nodularity converting into diffuse growth), but all the types have a tendency to progress to the more malignant HL. All the lymphocytic lymphomas dealt with here contain immature cells, in LLD-1, -2 and -3 of the IF-cell type, in LLD-4 and LLN morphologically somewhat different. It appears probable that the immature cells are the precursors of the lymphocytic lymphoma cells in all the conditions in question and that the eventual development of HL occurs when the immature cells have lost their ability to form lymphocytes and divide homoplastically.

Chapter 12

FINAL REMARKS ON NOMENCLATURE

No attempt will be made to suggest a new nomenclature for malignant lymphoma. The one used consists of practical working terms. Several research groups have recently suggested new nomenclature systems, see chapter 2. Many of those systems can be regarded as modifications of Rappaport's nomenclature. Lennert in Germany has devoted much work to this problem for a long time and he has somewhat modified his terms from time to time. At present, Lennert recommends the so-called Kiel classification, for which he is responsible to a great extent (20). Lukes & Collins' system (42) and the Kiel classification can be regarded as quite new approaches to the problem and my findings will be briefly discussed in relation to them. A detailed clinical trial should be undertaken before any new nomenclature is recommended for general use. As far as I know, no extensive clinical trial has yet been published where the Kiel classification and Lukes & Collins' classification have been tested and compared. Such studies are said to be in progress, and it is to be hoped that they will give unequivocal support to one system or the other, so that an international agreement may be reached. Rappaport's system has many disadvantages, but at present it has the great advantage of being well understood in most countries. Until an international agreement on a new system has been reached, I do not think there is any reason to change any local, deep rooted terminology, in which the clinicians and morphologists can converse. If such terms as reticulum cell sarcoma and lymphosarcoma are used, it would be necessary in scientific work to describe more exactly which morphological picture is intended.

As previously mentioned, Rappaport's well differentiated diffuse lymphocytic lymphoma includes both CLL and aleukemic cases. In several materials, the latter probably corresponds, at least partly, to what I have called LLD-3. My group LLD-2 is probably included in poorly differentiated, diffuse lymphocytic lymphoma. LLD-4, according to Rappaport, also should be called poorly differentiated, diffuse lymphocytic lymphoma. The small-cell cases and such with very few blasts are difficult to classify according to Rappaport and correspond to what, for example, Dorfman calls well or poorly differentiated diffuse lymphocytic lymphoma. LLN is nodular lymphocytic malignant lymphoma according to Rappaport. The term nodular is not recommended by Lukes & Collins or in the Kiel classification. In these systems "nodular" should be replaced by "follicular". This is based on the assumption that the nodules correspond to true follicles and germinal centers in normal lymphatic tissue. Much argues in favour of this view and the term follicular may be better though, to me, nodular is acceptable as a strictly morphologic description, while follicular infers a certain patho-physiologic aspect of the classification, which at present may be dubious.

Rappaport's classification also includes a group of well differentiated, lymphocytic lymphoma with morphologic manifestations of dysproteinemia. Some of the cases of LLD-3 and of macroglobulinemia should probably be included in this group, which, however, appears to be poorly defined morphologically.

Lukes & Collins' system has several chief groups according to the supposed physiologic character of the involved cells, for example, T-cell types and B-cell types. The B-cell types are those which are relevant in my study. The subdivisions thereof are small lymphocytic type (CLL), plasmacytoid lymphocytic type, follicular centre cell (FCC) type and immunoblastic sarcoma of B-cells. The FCC-type is further subdivided into small cleaved, large cleaved, small non-cleaved and large non-cleaved types. All of them may be follicular, diffuse, follicular and diffuse, and sclerotic. Sclerosis may be seen in many types of malignant lymphoma, but especially in such as I have called LLD-4 and LLN. It has been claimed to be a prognostically favourable sign but this aspect was not studied in my material as the cases were so few.

LLD-1 is small lymphocyte type (CLL). LLD-3 probably should be called plasmacytoid lymphocyte. In my opinion this is a misnomer as the tumour cells are not plasmacytoid in LLD-3 but lymphocytic cells, typical and atypical. Many plasma cells are seen in the nodes and other tissues, but it has not been proved that they are part of the tumour proliferation. The picture of macroglobulinemia, however, could be called plasmacytoid lymphocytic as intermediate cell forms are seen. My cases LLD-4 and LLN correspond to FCC-types, the small-cell cases of LLD-4 to small cleaved FCC-type and the large-cell LLD-4 cases to large cleaved FCC-type. Small and large non-cleaved FCC-types according to Lukes & Collins were not included in my study as they were referred to undifferentiated lymphoma and HL. Possibly, however, LLD-2 should have been referred to a non-cleaved type.

My cases of HL presumably should have been classified as immunoblastic sarcoma. Lukes & Collins' classification also includes a group of histiocytic lymphoma, however, but according to the authors this is not well defined from a pure morphological point of view.

It is thus evident that my groups have a close correspondance to those of Lukes & Collins' classification. But I feel that the term plasmacytoid lymphocytic is not well chosen. My material was not large enough to warrant any conclusions as to whether it is meaningful to distinguish small-cleaved from large-cleaved lymphoma types.

The entities of the Kiel classification relevant to this study are the following.

A. Malignant lymphoma of low grade malignancy.

1. Malignant lymphoma, lymphocytic. This group generally corresponds to CLL of the B-cell type. The PAS-reaction is by definition negative.
2. Malignant lymphoma, lymphoplasmacytoid (immunocytic). Lennert subdivides this group in three: lymphoplasmacytic, lymphoplasmacytoid, and polymorphous. Most cases of immunocytic malignant lymphoma reveal PAS-positive globular inclusions in the cells.
3. Malignant lymphoma, centrocytic.
4. Malignant lymphoma, centroblastic/centrocytic. This group includes all

follicular lymphomas.

B. Malignant lymphoma of high grade malignancy.

1. Malignant lymphoma, centroblastic.
2. Malignant lymphoma, lymphoblastic.
3. Malignant lymphoma, immunoblastic.

Some of my cases LLD-1 correspond to malignant lymphoma, lymphocytic. However, the PAS-reaction in this group is, according to Lennert, by definition negative. Thus, some of my cases LLD-1, which contained PAS-positive lymphocytic cells, must by needs be referred to malignant lymphoma, lymphoplasmacytoid (immunocytic). I do not think that this is reasonable. Some of the cases like 258/68 (see fig. 161, 162) were clinically very characteristic CLL, and corresponded exactly to Lennert's descriptions of malignant lymphoma, lymphocytic. A very occasional cell with PAS-positive globules of quite characteristic type was found, however. The patient had low immunoglobulin levels and no monoclonal component. Thus, the case should be referred to malignant lymphoma, lymphoplasmacytoid (immunocytic) of the Kiel classification only because of the occurrence of such PAS-positive cells. They may have to be searched for in many sections before found, and I do not think that this single criterion is useful for a classification. Instead, I think that the occurrence of IF is more appropriate for defining a group of lymphocytic lymphomas corresponding to the clinical picture of CLL. It would include some cases with monoclonal immunoglobulin components within CLL. According to Lennert, monoclonal immunoglobulin components also by definition exclude CLL. Lennert's opinion thus is that electrophoretic or histochemical demonstration of monoclonal immunoglobulin production is not compatible with CLL. As far as I can see, it has not been proved that all the tumour cells must be either producing or non-producing. If a very occasional cell can produce immunoglobulins, such a distinction as made by Lennert is not useful and the difference between the two groups in question will be only relative. But, I also feel that LLD-1 and LLD-3 are closely connected conditions and it may well be that occasional cases have an intermediate morphology though my material did not present completely examined cases of such intermediate morphology. Cytologically, however, the cases of bone marrow group 1-3 were intermediate in type and also clinically, and they may well represent such conditions. Thus, I think that there are no strict boundaries between LLD-1 and LLD-3 or between the groups malignant lymphoma lymphocytic and malignant lymphoma lymphoplasmacytoid (immunocytic) of the Kiel classification. According to Lennert, the cell content of malignant lymphoma lymphoplasmacytoid (immunocytic) well corresponds to that of my group LLD-3 and atypical cells are described.

One of my cases of LLD-3 (1147/65) in the biopsy specimens had a picture, which corresponded well to the subgroup lymphoplasmacytic, while the necropsy specimens were of type polymorphous. Thus, this type is, or may be, a later phase of the lymphoplasmacytic type. It is reasonable to assume that it is a developmental stage towards HL(malignant lymphoma, immunoblastic).

According to Lennert, the characteristic picture of Waldenström's macroglobulinemia is the malignant lymphoma with lymphoplasmacytic cellular picture. That

is, clear lymphocytic and clear plasmacytic cells are present, but no intermediate forms. This was not the case in my material, where all the classical cases of Waldenström's macroglobulinemia had a cell series with a smooth line of transition between lymphocytes and plasma cells. None of my cases with the picture corresponding to malignant lymphoma, lymphoplasmacytic (LLD-3) had macroglobulinemia.

Malignant lymphoma, centrocytic corresponds in some respects to the group of FCC-lymphoma, small cleaved type in Lukes & Collins' classification. However, this group in the Kiel classification does not admit the presence of any blastic cells at all. No such tumours were found in my material but the 2 cases of LLD-4 with few blasts otherwise resembled this group of the Kiel classification.

Malignant lymphoma centroblastic/centrocytic corresponds to all the other cases of LLD-4 and LLN. It appears reasonable to have a common denomination for these processes, with a specification of whether diffuse or follicular, as the cellular content appears to be the same. However, the diffuse variant is probably much more often combined with leukemia. Also, the nodular variant may be more prone to develop HL.

The high grade malignant lymphomas of the Kiel classification correspond to Rappaport's groups of undifferentiated lymphoma and HL. Malignant lymphoma, lymphoblastic includes most cases of undifferentiated lymphoma. Malignant lymphoma centroblastic is the highly malignant growth developing in terminal phases of nodular lymphomas, thus what I have included in the term HL in the course of LLN. However, it should be observed that the case of LLD-4 which developed HL had a characteristic immunoblastic picture. Thus, one can not generalise and say that malignant lymphoma centroblastic always represents the end phase of malignant lymphoma centroblastic/centrocytic and malignant lymphoma immunoblastic the end phase of malignant lymphoma lymphocytic or lymphoplasmacytoid. But no case of my LLD-1, -2 or -3 developed a picture of the type malignant lymphoma centroblastic, and it is probably the characteristic picture of the terminal phase of nodular lymphomas.

Except for the cases resembling Hodgkin's disease, all those called HL in the groups LLD-1, -2 and -3 were partly of the type malignant lymphoma, immunoblastic. The Kiel classification also acknowledges the existence of true histiocytic lymphomas, but they are not definable on a strict morphological basis.

The Kiel classification does not include any group corresponding to LLD-2.

Thus, my scheme agrees with the Kiel classification in that LLD-4 and LLN are variants of the same process, and that there is usually a certain difference between the anaplastic tumours developing after these conditions and after other lymphocytic lymphomas. But I disagree with the Kiel classification in that CLL can be excluded morphologically by the presence of PAS-positive lymphocytic cells, at least when they occur in small numbers.

In Lennert's opinion most, but not all cases of CLL have a "pseudo-follicular" histologic picture. My group LLD-1 was defined by the IF. There was no lymph node biopsy without IF from a case clinically judged as CLL. As has been pointed out, IF may be difficult to detect in necropsy specimens. But in all the cases of

LLD-1 in the necropsy series, occasional IF or IF-like structures could be found in some sections, though not in every section. I therefore feel that IF are constant structures in CLL, but it may be true that not every node in every case contains evident IF. Thus, it may be possible that occasional biopsied nodes in clinically CLL-cases may lack evident IF though the case belongs to LLD-1. Nevertheless, I think that prolymphocytes and IF-cells can always be found and the slight or absent atypia of the mature cell component should always make it possible to distinguish LLD-1 from LLD-3 in biopsy specimens.

The presence of monoclonal immunoglobulin components excludes CLL in the Kiel classification. In many of my cases of LLD-1 (also without PAS-positive lymphocytic cells) no monoclonal component was found initially, but it appeared later on. According to the Kiel classification, such cases should thus be called malignant lymphoma lymphocytic, converting into malignant lymphoma lymphoplasmacytoid (immunocytic). This appears cumbersome and unnecessary.

The terminological problems bearing on macroglobulinemia are complicated. In the early phases of this disease the lymph nodes are generally not enlarged and it is a question primarily of a bone marrow infiltration. Generally, however, there is some slight infiltration of the nodes and they may be somewhat enlarged later on. From a practical point of view it may be unsuitable to designate the disease as a malignant lymphoma. But this is a semantic question. I seriously doubt the existence of Waldenström's macroglobulinemia without bone marrow infiltration. The disease could certainly be called lympho-proliferative. The characteristic cytologic picture is a mixture of lymphocytes, plasma cells and intermediate forms. No cytologic picture of this very type was found in any bone marrow smear in my series without the clinical picture of Waldenström's macroglobulinemia. It cannot be excluded that occasional such cases exist, but they must be rare. As pointed out above, I think that plasmacytoid lymphocytic lymphoma (Lukes & Collins) is an acceptable description of the picture. In the Kiel classification it could be called malignant lymphoma, immunocytic of lymphoplasmacytoid type, but should not be designated lymphoplasmacytic type. Waldenström's macroglobulinemia should be used as a designation for a biochemical abnormality and a clinical syndrome and not as a morphologic diagnosis. The morphologic examination of the condition will presumably also in the future be performed primarily by cytologic examination of the bone marrow. One may perhaps use the term "cytology of immunocytoma type with a picture compatible with Waldenström's macroglobulinemia". Anyhow, it appears that the disease is a malignant condition of lymphocytic cells closely related to other forms of lymphocytic malignant lymphoma. The clinical features justify the retention of the term Waldenström's macroglobulinemia even if it should not be used as a morphologic diagnosis.

SUMMARY

This study concerns the interrelationship between lymphocytic malignant lymphoma and lymphatic leukemia and an investigation of the morphologic and clinical course of some types of lymphocytic lymphoma and leukemia from the time of diagnosis to death. Cases with Waldenström's macroglobulinemia were also studied.

A historical review is given of the lymphoma-leukemia problem complex as well as of the literature on terminal transformation to other types of lymphoma in chronic lymphatic leukemia (CLL), and other types of lymphocytic malignant lymphoma. A brief outline is presented of different opinions of the nature of Waldenström's macroglobulinemia.

The material consisted of necropsied cases of malignant lymphocytic diseases in adults from Malmö (population about 250,000) during 17 years.

A simple lymphoma nomenclature based on Rappaport's well-known terms was used. The term "differentiation" was, however, excluded. The following chief groups were used: lymphocytic malignant lymphoma, diffuse (LLD), lymphocytic malignant lymphoma, nodular (LLN), malignant lymphoma of histiocytic type (HL).

LYMPH NODE BIOPSY STUDY. The lymphocytic lymphomas were studied histologically in a biopsy series of 41 cases. They were assigned to the following groups:

LLD-1: this was found to be the characteristic picture in CLL. Histologically, the node consisted mainly of small lymphocytes with no apparent abnormalities. There were, however, foci of immature cells (immature foci, IF) made up of larger cells with nucleoli but still with a lymphocytic character. They were called prolymphocytes. Further, the IF contained still larger cells with very prominent, centrally situated nucleoli.

LLD-2: these nodes were dominated by prolymphocytes and also contained the larger cells of the IF described above, but no evident IF as this immature tissue made up the whole node. The picture was interpreted as corresponding to the hematologic condition called prolymphocytic leukemia.

LLD-3: the cells were of the same size as the small lymphocytes of LLD-1, or slightly larger. The mature cell component was always somewhat atypical. Immature cells similar to those described above were present but they were also generally somewhat atypical and no IF were present.

LLD-4: the dominating cell was lymphocytic in type but had an irregularly shaped nucleus (such cells were called atypical). Also larger, blastic cells were present, but they differed in appearance from those in the preceding groups.

LLN: tumours with well-formed nodules resembling true follicles of normal lymphatic tissue. The nodules had a cell content similar to that of LLD-4.

The distribution among the groups was as follows:

LLD-1 :	13 cases
LLD-2 :	2 cases
LLD-3 :	7 cases
LLD-4 :	13 cases
LLN :	<u>6 cases</u>
Total :	41 cases

The age and survival of the different types are given. The groups were too small to reveal any statistically significant differences.

LLD-1 always appeared to be a systemic disease when diagnosed. This also applied to LLD-2. LLD-3 also generally appeared to be generalised but in occasional cases the bone marrow was spared. LLD-4 and LLN often appeared to have a localised stage before dissemination.

The leukemic manifestations of the various groups are described. LLD-1 always was leukemic at the time of the diagnosis. One of the 2 cases of LLD-2 was non-leukemic. None of the cases of LLD-3 was leukemic at the time of diagnosis, but 4 of 7 had absolute lymphocytosis. LLD-4 generally was without abnormal values in this respect but a few cases had leukemic values and some others had absolute lymphocytosis without leukemic values of the WBC. Five of 6 cases of LLN had normal blood values, only 1 had absolute lymphocytosis and none was leukemic.

During some period in the course of the disease all cases of LLD-1 and LLD-2 were leukemic, while 4 of 7 cases of LLD-3 had clearly leukemic values and 6 of 7 had absolute lymphocytosis during some period. In LLD-4 8 of 13 had leukemic values during some period and 10 of 13 had absolute lymphocytosis during some period. In LLN no patient had clear leukemia but 2 had absolute lymphocytosis during some period.

All the patients in LLD-1 and LLD-2 had bone marrow infiltration at necropsy, and the majority but not all of the cases in the other groups.

The cytologic appearance of the blood and the bone marrow in the various groups is described.

The immunoglobulin values in the clinical records were examined. The characteristic finding in LLD-1 was low values, while all the examined cases of LLD-3 initially had high values. Monoclonal immunoglobulin components were seen in both groups. In the other groups the immunoglobulin values were less consistent.

All the cases had been examined with a complete necropsy. Generalised involvement was the rule in LLD-1 and -2. The majority of cases of LLD-3 also had generalised lesions at necropsy though in occasional cases the bone marrow and occasional nodes seemed to have been spared. No soft tissue or parenchymatous tumours were seen in LLD-1, -2 or -3.

In LLD-4 disseminated disease was also generally found at necropsy, but occasional cases had no infiltration of the spleen or liver. Some also had normal lymph nodes in some sites. Many cases had extra-lymphatic tumours.

All the cases of LLN had had lymph node engagement in all sites at the time of death. Spleen, liver and bone marrow were spared in some cases. Most of the cases had extra-lymphatic tumours.

Some case histories are related to illustrate the natural history of the lymphoma groups. It is concluded that LLD-3 often had a prolonged prediagnostic stage during which the blood picture was normal or almost normal. Later on the majority of cases developed atypical lymphocytosis and many a clearly leukemic picture. Many of the patients developed HL before death.

Some of the cases of LLD-4 also appeared to have a prolonged pre-stage with few or no clinical symptoms. Cases with small lymphocytic cells and few blasts appeared to have the best prognosis. A leukemic blood picture sometimes occurred and lasted for more than 2 years, but in most cases such a blood picture appeared only during the last few months of life.

Also some cases of LLN reported a long preclinical history. HL often developed terminally in this group.

The findings were interpreted as follows. LLD-1 (CLL) and LLD-2 (prolymphocytic leukemia) are closely related, systemic diseases ("lymphocytic leukemias proper"). LLD-4 and LLN are variants of the same disease ("the lymphocytic lymphomas proper"). LLD-4 is probably seen more often with a leukemic blood picture, however. LLD-3 is difficult to classify as either lymphoma or leukemia and appears to occupy an intermediate position. A division of the lymphocytic malignant diseases into leukemia and lymphoma is not very useful. In the leukemic phase, LLD-3 had many similarities to CLL, but regarded as groups, there were many differences between the 2 conditions.

EXAMINATION OF BONE MARROW SMEARS INTERPRETED AS LYMPHATIC LEUKEMIA OR LYMPHOCYTIC LYMPHOMA. In 79 of the necropsy cases technically acceptable smears of bone marrow obtained during life were available. They were studied in May-Grünwald-Giemsa staining. A group (bone marrow group 1) was judged as characteristic of CLL, based on a predominance of apparently normal or almost normal lymphocytes mixed with a low percentage of prolymphocytes.

A group (bone marrow group 2) was distinguished where more than 50 % of nucleolated lymphocytic cells of prolymphocytic type were seen. A group of smears (group 3) was judged as lymphocytic lymphoma of non-leukemia type. It was found difficult to distinguish the pictures of LLD-3, LLD-4 and LLN with certainty and they were pooled in one group, which also included some cases with a similar bone marrow picture, but with the histologic picture of undifferentiated lymphoma in biopsy or necropsy specimens.

A group of smears (group 4) probably represented Waldenström's macroglobulinemia as judged from cytologic characteristics described in the text.

Occasional cases could not be classified in any of the above mentioned groups. Some cases appeared to be intermediate CLL and group 3 (group 1-3).

Forty-two cases were judged as CLL (group 1). Clinically, they were all leukemic at the time of the diagnosis and all of them had the clinical diagnosis of CLL. Figures for age and survival were approximately the same as for LLD-1 in the lymph node biopsy material. Some of the cases had HL or Hodgkin's disease in the necropsy specimens. No clinical or hematologic parameters could be detected to warrant a distinction of those cases from other cases of CLL.

Generalised lesions in the necropsy specimens was the rule. Occasional cases had tumorous collections of lymphocytes outside the lymphatic system.

Group 2 (12 cases, suspected as prolymphocytic leukemia) did not clinically differ perceptibly from group 1. There was a higher percentage of cases with many immature cells in the peripheral blood, but some cases had a fully mature blood picture. Generalised lesions at necropsy was the rule. Three of the cases had a remarkable picture in the necropsy specimens with myelofibrosis with diffuse lymphocytic infiltration. Also the extramedullary infiltrates showed signs of fibrosis.

The cases cytologically difficult to classify as either CLL or lymphocytic malignant lymphoma of non-leukemic type had no clinical characteristics in common. They resembled either the type of disease seen in LLD-1 or LLD-3.

All the cases judged as suspect Waldenström's macroglobulinemia had this clinical diagnosis.

The group judged as lymphocytic lymphoma of non-leukemia type was difficult to separate into LLD-3, LLD-4, LLN or undifferentiated lymphoma (in Rappaport's nomenclature). As a general rule, the undifferentiated lymphomas had a higher percentage of purely blastic cells, but many cells with clearly lymphocytic features were also present, and the blood picture may be lymphocytic, though atypical. The most characteristic feature of LLD-4 and LLN was a highly irregular shape of the nuclei, but apparently normal lymphocytes may also be found. Cytologically, the border towards LLD-3 was diffuse. The smears from non-leukemic lymphocytic lymphomas were often technically poor, making it even more difficult to distinguish the said conditions from each other.

It is concluded that the lymphocytic leukemias and Waldenström's macroglobulinemia can be diagnosed with reasonable certainty from routinely stained bone marrow smears. In cases judged as non-leukemic lymphocytic malignant lymphoma, exact classification of the bone marrow picture is difficult if not impossible. Classification of such cases requires lymph node biopsy.

TOTAL NECROPSY MATERIAL. Sixty patients were not examined with either biopsy of the lymph node or bone marrow aspiration. The majority, 45 cases, were judged as LLD-1. Only 2 cases were judged as LLD-3. Technical difficulties are met with in the classification of the diffuse lymphomas in necropsy specimens if autolysis has taken place. Generally, however, correct classification will be possible if many sections are examined.

Broadly speaking, the findings in the necropsy material confirmed what had been found in the series of lymph node biopsies and bone marrow smears. The reason for the difference in the prevalence figures among the groups in biopsy and necropsy series is discussed. It is proposed that LLD-3 is seen much less often in necropsy series than in biopsy series because a large number of such cases have transformed to HL before the death of the patient.

Among cases clinically judged as CLL the frequency of malignant tumours of non-lymphatic type did not differ significantly from that of the entire necropsy material of the institute.

A SERIES OF CASES CLINICALLY DIAGNOSED AS WALDENSTRÖM'S MACROGLOBULINEMIA. Nine cases had this clinical diagnosis. Six of them had a classical bone marrow cytological picture. They were clinically very benign. One of them died after 180 months of HL. Lymph node enlargement was otherwise not a feature of the disease, though most, but not all, of the patients had microscopic lymph node lesions at necropsy. The histologic picture resembled LLD-3 but the cytologic picture was different in that only few or no atypical immature cells were seen and the nodes were dominated by lymphocytes, plasma cells and intermediate cell-forms. Occasional immature cells were always seen.

Three cases with a clinical diagnosis of macroglobulinemia deviated considerably from the above cases. One of them had a plasmacytoid and blastic, focal proliferation in the bone marrow, but no lesions of the lymph nodes. Another one had the blood picture of CLL, but a histologic picture of the tissues compatible with other cases of macroglobulinemia. At splenectomy, a small focus of HL was found in the spleen. In another patient, the disease was clinically characterised primarily by pulmonary infiltration. This patient had 3 monoclonal immunoglobulin components, IgM, IgG and IgA. In the bone marrow there were focal infiltrates with central fields of lymphocytic cells, surrounded by fields of plasmacytoid cells and plasma cells.

It is concluded that most cases of Waldenström's macroglobulinemia have a characteristic cytologic picture of the bone marrow. Lymph node enlargement is not a feature of the early phases of the disease. Occasional cases with this clinical diagnosis have morphologically deviating features. Hematologically, a picture of CLL may be seen. The morphologic picture of the tissues is still lymphoplasma-cytoid, however. Thus, Waldenström's macroglobulinemia cannot be used as a morphologic diagnosis. The picture of the tissues is mostly, but not always, of a lymphoplasmacytoid type. HL may develop terminally in macroglobulinemia, probably not so rarely. Macroglobulinemia should be regarded as a malignant lympho-proliferative disease closely related to other lymphocytic malignant lymphomas, but in the early phases it is primarily a disease of the bone marrow.

A STUDY OF THE IMMATURE CELLS IN LLD-1. IF varied widely in size and number in the lymph nodes. They contained mature lymphocytes, prolymphocytes, which were generally the dominating type of cell, a moderate amount of larger, round cells with a prominent, centrally situated nucleolus and moderately basophilic cytoplasm (called IF-2 cells). Further, an occasional very large, strongly basophilic cell with many large nucleoli was seen (called IF-1 cell).

All the cases with IF in the series had a leukemic blood picture at the time of the diagnosis. IF were therefore regarded as characteristic of CLL. The amount of IF, however, was not directly related to the values found for WBC in the peripheral blood, nor was the amount of the above mentioned immature cell types in the bone marrow directly related to the level of the WBC. Cases with a high percentage of immature cells in the peripheral blood had a tendency to reach very high maximal values of WBC and had a worse prognosis than cases with predominantly mature blood picture. They corresponded approximately to the prolymphocytic leukemia

of the literature. This hematologic picture may be seen in LLD-2, but probably also in LLD-1 with large IF. LLD-1 (CLL) and LLD-2 (prolymphocytic leukemia) are interpreted as variants of the same disease.

For technical reasons IF were sometimes difficult to detect in necropsy specimens. However, they were generally demonstrated when many tissue sections were examined in cases hematologically characteristic of CLL. Sometimes very prominent, IF-like foci with large and atypical cells were seen in necropsy specimens from such cases. They were called IF-necropsy (IF-n). Such foci were seen in 24 of 94 CLL-cases. IF-n showed no sharp border with microscopic HL-lesions. IF-n were primarily seen in central lymph nodes and the liver, not so often in the spleen or the bone marrow and seldom in other tissues. IF-n were primarily seen in very large nodes and large tissue infiltrates in the liver. All cases with IF-n in the liver and in the spleen had marked enlargement of these organs.

Cases demonstrating IF-n in the necropsy specimens had no clinical or hematologic characteristics differing from those of other cases in the series. In the vast majority of cases where IF-n were found the patients had died of lymphoma, but in those who died from some other cause IF-n were seen in only few cases. The average survival of cases with IF-n was longer than that of cases without such lesions and it is concluded that IF-n are a sign that the disease had approached its natural terminal phase. Monoclonal immunoglobulin components were seen more often in cases with IF-n in the necropsy specimens than in others. Such monoclonal components often occurred only late in the course of the disease. It is concluded that the appearance of a monoclonal component in CLL may be a bad prognostic sign.

A STUDY OF CASES WHICH DEVELOPED MALIGNANT LYMPHOMA OF HISTIOCYTIC TYPE IN THE COURSE OF CHRONIC LYMPHATIC LEUKEMIA. In the CLL series of 94 cases, necropsy revealed Hodgkin's disease in 2 and HL in 10. For practical reasons, the cases of Hodgkin's disease are included within the scope of the term HL below.

The HL-cases did not survive a shorter time after the diagnosis than other cases in the series. Only in 2 of the patients the diagnosis was made before necropsy. Clinically, the cases were characterised by a very rapid downhill course during the last year before death. Fever was almost universally seen. The organ affected by HL at necropsy had always grown rapidly in the final phase. No signs could be detected of any special type of treatment having precipitated the development of HL. There was no characteristic hematologic reaction pattern to treatment of CLL in those cases which eventually developed HL. Most of the cases were still leukemic at the time of death. Monoclonal immunoglobulin components were common among the patients developing HL. One of the patients also had characteristic multiple myeloma.

Symptomatic HL-lesions often appeared in the throat or air passages. However, it is concluded that HL transformation probably takes place in many sites in the body at approximately the same time in most cases. Extra-lymphatic tumorous lesions generally developed. The liver was affected more often than the spleen or the bone marrow. At least one of the HL-cases had a morphologic picture characteristic of Hodgkin's disease and another one a picture best fitting in with the dia-

gnosis of Hodgkin's disease, though somewhat atypical. Otherwise, the HL-cases histologically and cytologically were primarily of so-called immunoblastic type. Three of the cases, however, morphologically were suspect of "histiocytic" differentiation of the cells.

In the other lymphoma groups of the necropsy series, also HL-cases were seen. LLD-3 appeared to be the group most often affected by this terminal complication. Also in this group the cases were primarily of immunoblastic malignant lymphoma type, but a case with a picture suspect of Hodgkin's disease was seen. The clinical picture in the terminal phase of the disease was similar in this group to that of the LLD-1 cases developing HL.

One of the LLD-4 cases also developed HL of typical immunoblastic type. This case from the beginning had some similarities to LLD-3.

HL was seen in 6 of 13 cases of LLN. These cases are not described in detail.

SPECIAL MORPHOLOGIC STUDIES OF IF AND HL. Some special staining methods were used in cases of HL and LLD-1. They were not very rewarding. PAS-positive inclusions within lymphocytic tumour cells may be seen also in cases otherwise quite characteristic of LLD-1 (CLL) and in the absence of monoclonal immunoglobulin components.

Electron microscopic investigation of the IF demonstrated very complex surface relations between the cells with intertwining processes. They were sometimes connected by desmosomes in the IF-2 cells. IF-2 cells contained occasional strands and whorls of granular endoplasmic reticulum. IF-1 cells were found only after prolonged search. They were electron microscopically characterised by many free ribosomes and polyribosomes.

Another cell type was seen, which had similarities to IF-2 cells and which was difficult to distinguish from such in the light microscope. It had a polarised cytoplasm with extensions with desmosomes and resembled in some respects reticulum cells.

An electron microscopic study of some cases which had developed HL was performed. The cells had similarities to IF-cells but were more anaplastic. Some similarities to reticulum cells were also seen.

In the DISCUSSION 2 questions are primarily dwelt upon, namely whether there is any connection between the immature cells of the IF and the mature lymphocytes of CLL. It is concluded that there probably is and that the IF-1 cell should be regarded as the "first" cell in the CLL-process and that IF-2 cells and prolymphocytes are descendants thereof. It is proposed that the IF-1 cell is a pathologic immunoblast and an immigrant to the node through the lymph node vessels. Thus, the mature lymphocytes of CLL should be B:2 cells. What is the B:1 cell is speculative.

Further, it is discussed whether there is any connection between the IF and the terminal development of HL. It is concluded that such a connection exists and that the HL-cells are the IF-cells "in malignant degeneration". It is proposed that the assumed pathologic immunoblasts (IF-1 cells) have several developmental possibilities. One of them is the possibility to produce small lymphocytes (the mature cell component of CLL), another possibility is to differentiate into immunoglobu-

lin producing cells. This might explain the appearance of monoclonal immunoglobulin components when HL is developing. Further, it is speculated that the IF-1 cell may have a possible pathway towards reticulum cells, possibly of the dendritic type, or towards macrophagic cells. This might explain a morphologic "histiocytic" tendency and a fibroblastic tendency in some of the HL-cases developing in the final phase of CLL.

The findings are discussed in relation to some new nomenclature systems of malignant lymphomas.

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MICROSCOPIC REPRODUCTIONS

Unless otherwise stated, all cytologic specimens were stained with May-Grünwald-Giemsa and the illustrations of them are magnified 1120 x, and all illustrations of histologic appearances are of specimens stained with hematoxylin and eosin.

The electron microscopic photographic recording was done on cut film in a Philips 300 electron microscope. All electron microscopic enlargements are approximate.

The necropsy number of the case to which the illustration refers is given only if the case is described in the text.

Fig. 1. Low power view of lymph node in LLD-1 with large immature foci (IF). The IF appear as lighter fields. Case 829/69. Giemsa, x 30.

Fig. 2. Transitional zone between IF (to the right) and mature part (left). Note difference in cell size between the prolymphocytes, which dominate the right side of the reproduction, and the mature lymphocytes to the left. Large immature cell at asterisk. IF-1 cell (see chapter 8) at arrow. Mitotic figures left centre. They are often most numerous in the periphery of the IF. Case 829/69. Giemsa, x 540.

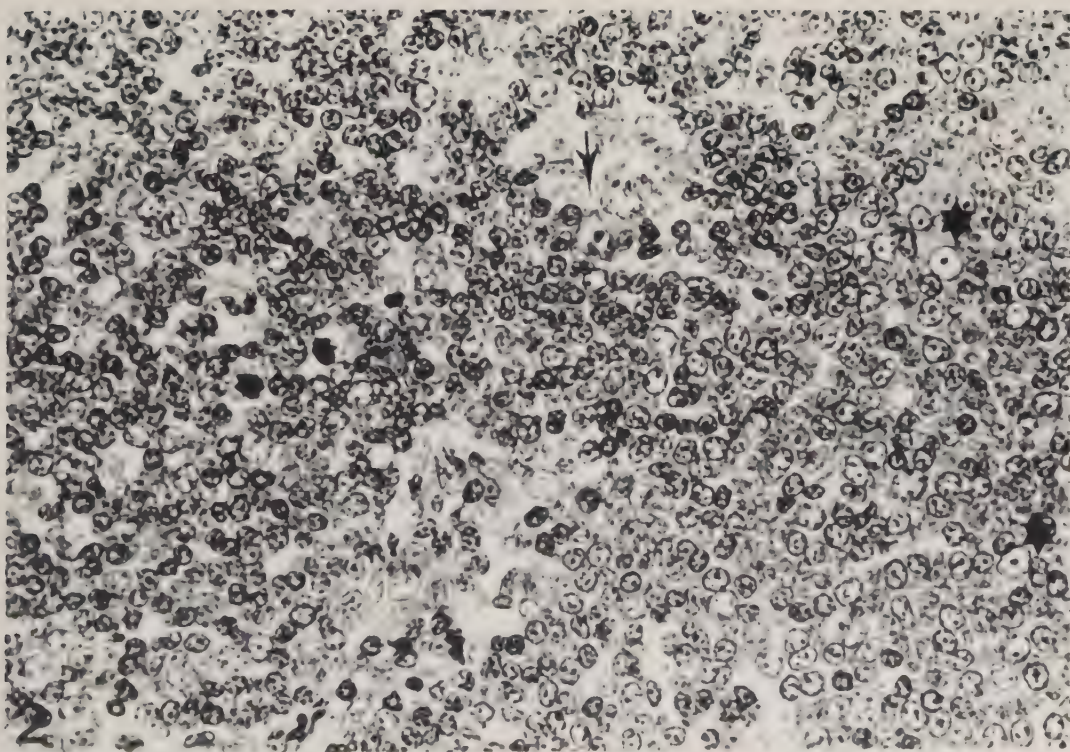
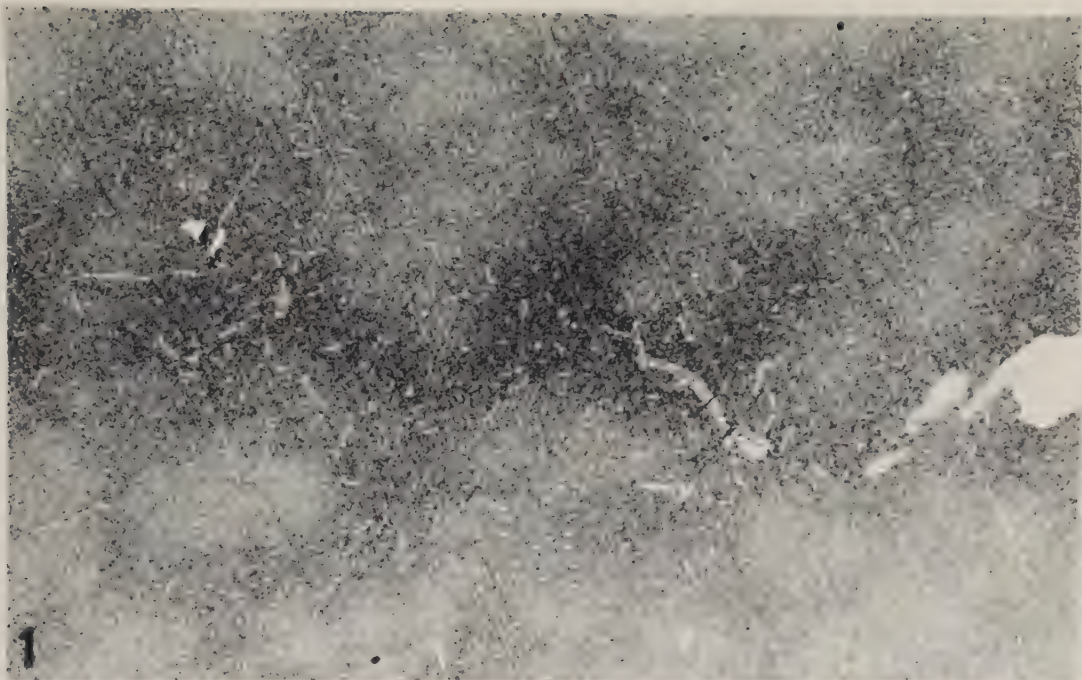


Fig. 3. LLD-1. Mature part. The picture is dominated by small, mature lymphocytes. Only occasional prolymphocytes. Biopsy case 2-219. x 1120.

Fig. 4. LLD-1. Cell content of IF. Several large immature cells (IF-2 cells, see chapter 8) are seen, e.g. at asterisk. Most other cells are prolymphocytes (e.g. at arrows). Occasional mature lymphocytes. Biopsy case 2-219. x 1120.

Fig. 5. Blood smear with lymphocytes and a prolymphocyte from case with LLD-1 (185/63).

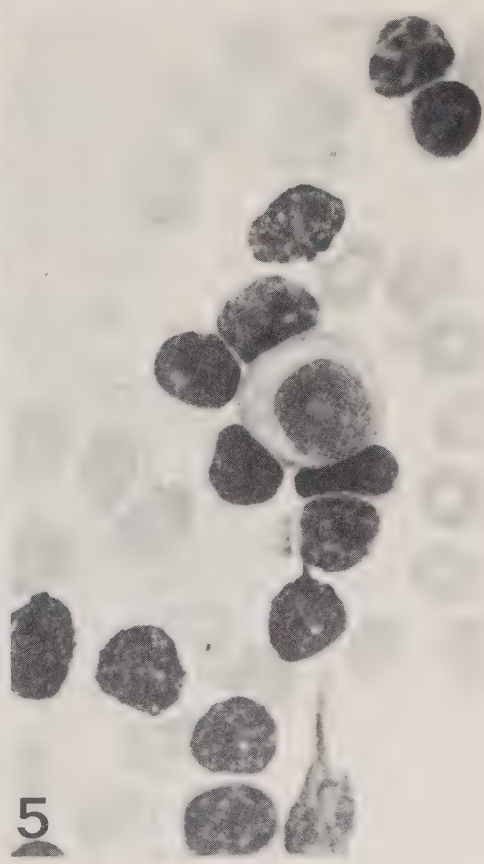
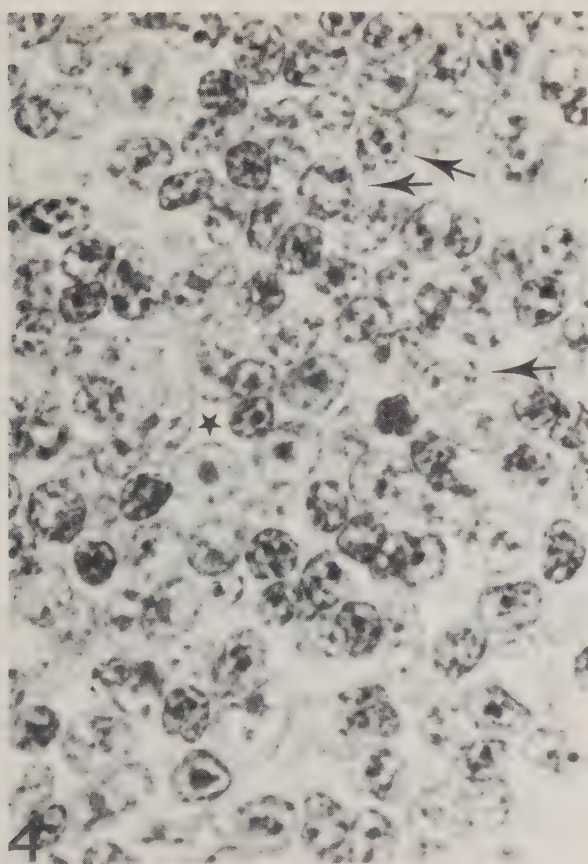
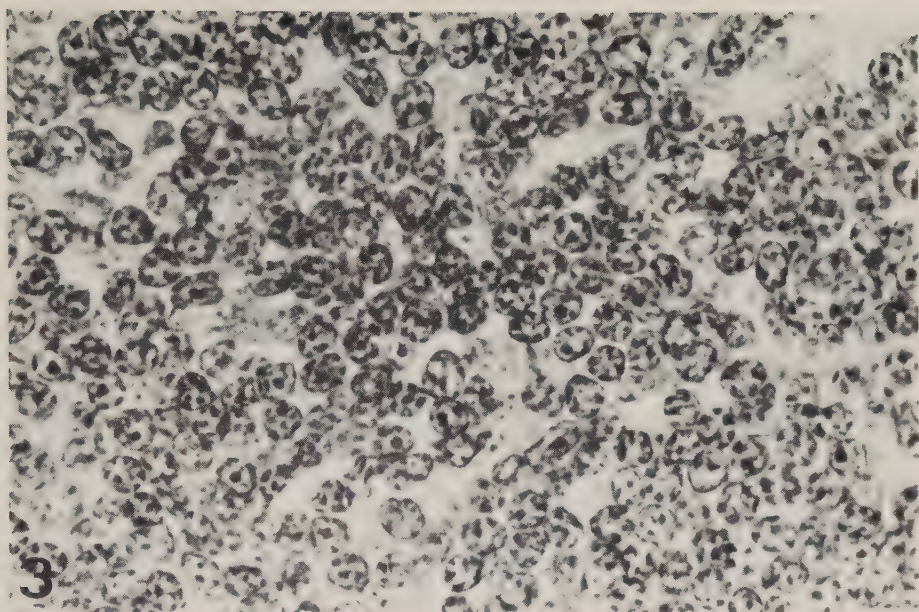


Fig. 6. Bone marrow smear from case with LLD-1 (185/63). Lymphocytes, prolymphocyte and large immature cell.

Fig. 7. Smear of fine needle aspirate of lymph node in LLD-1.

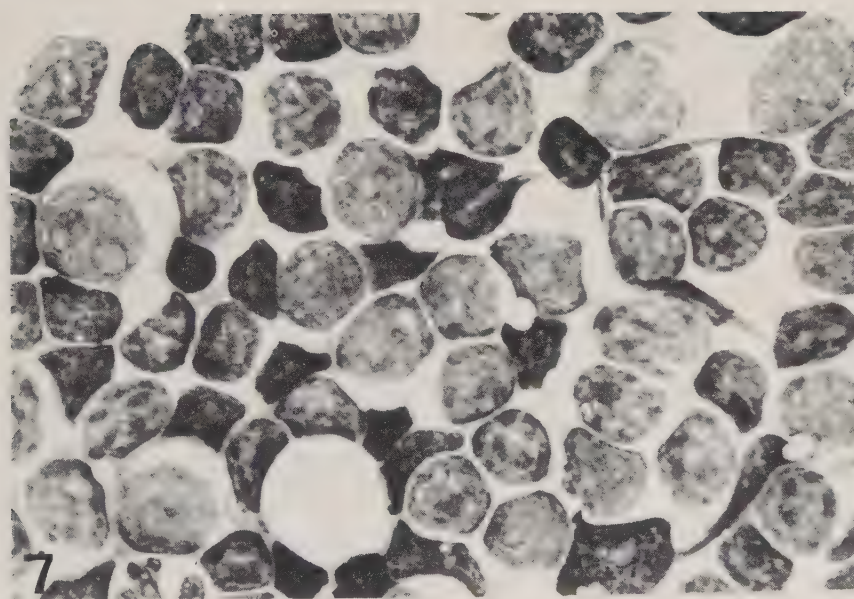
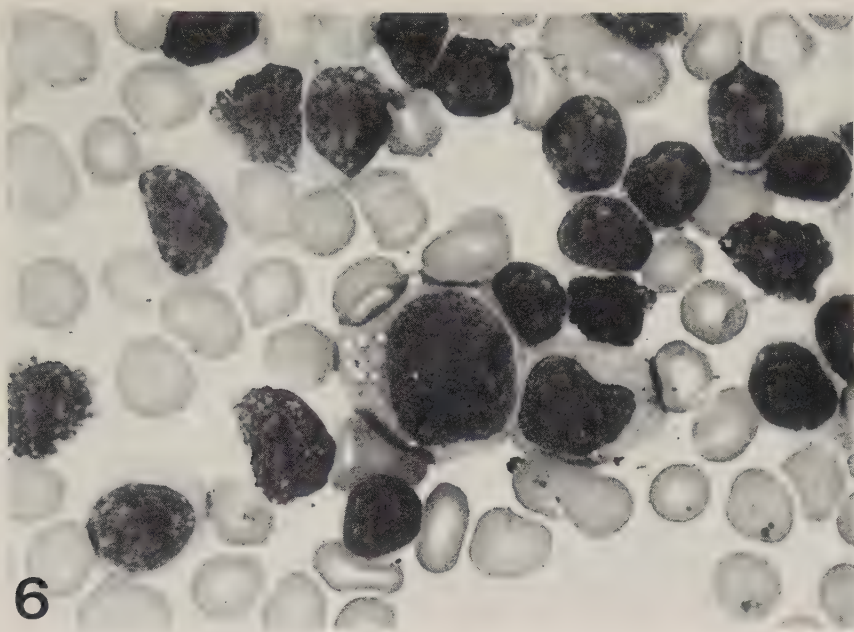


Fig. 8. Section of aspirated bone marrow particle in LLD-1, demonstrating diffuse infiltration with predominantly mature lymphocytes without IF. Large cells are megakaryocytes. Some remaining fat cells. Case 31/67. x 450.

Fig. 9. Higher magnification of bone marrow section from case 31/67 (LLD-1), demonstrating an occasional prolymphocyte and large immature cell (centre) scattered among mature lymphocytes. x 1120.

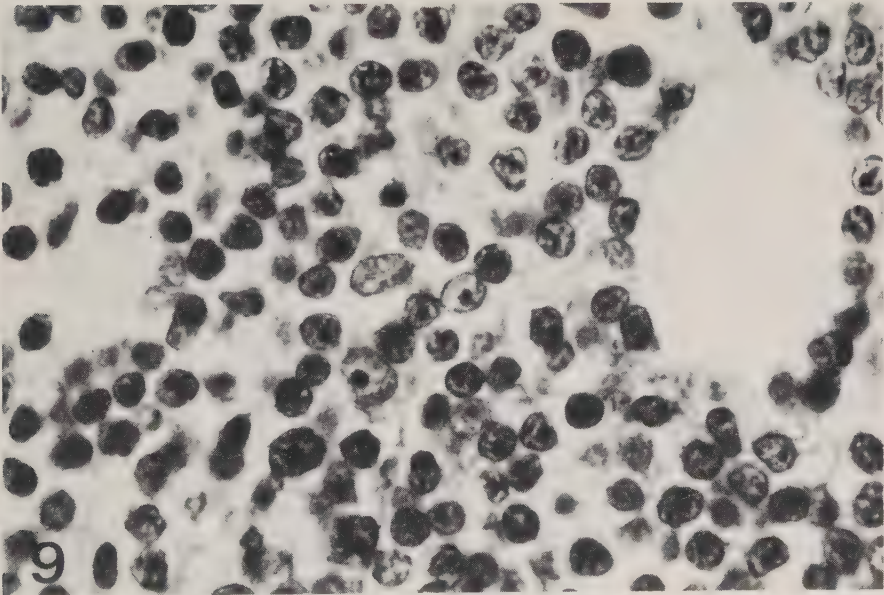
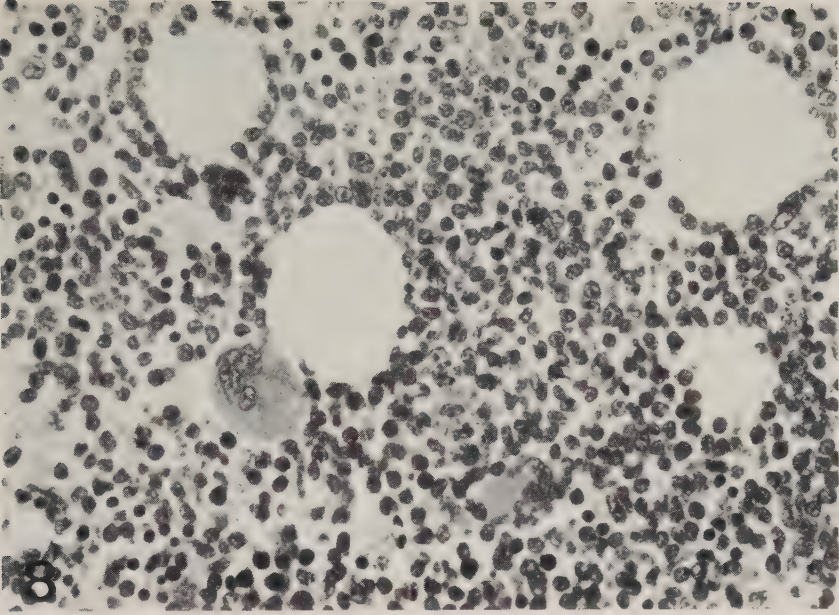


Fig. 10. LLD-2. Section of lymph node demonstrating large immature cells and predominance of prolymphocytes but only few mature lymphocytes. Mitotic figure to the left. Case 663/58. x 1120.

Fig. 11. Fine-needle aspirate from the same node as in fig. 10.

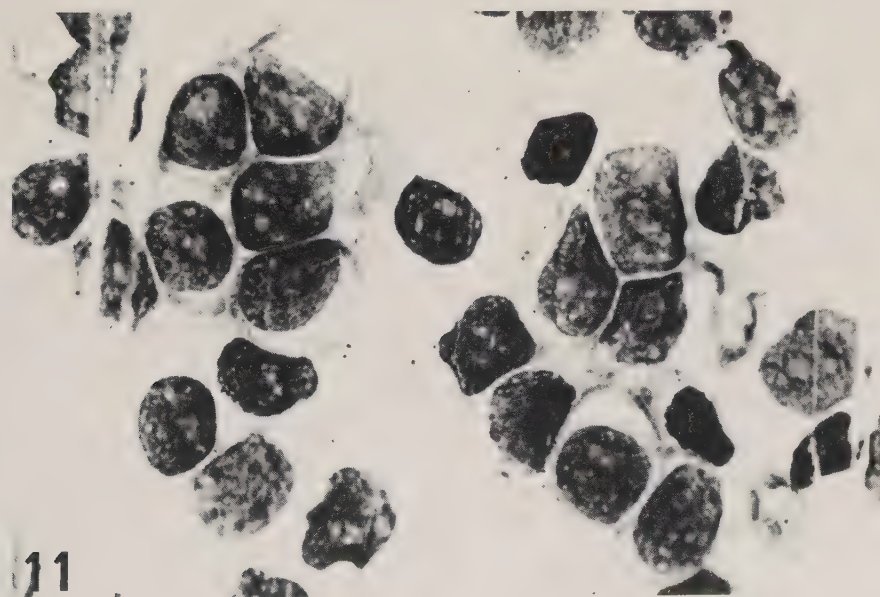
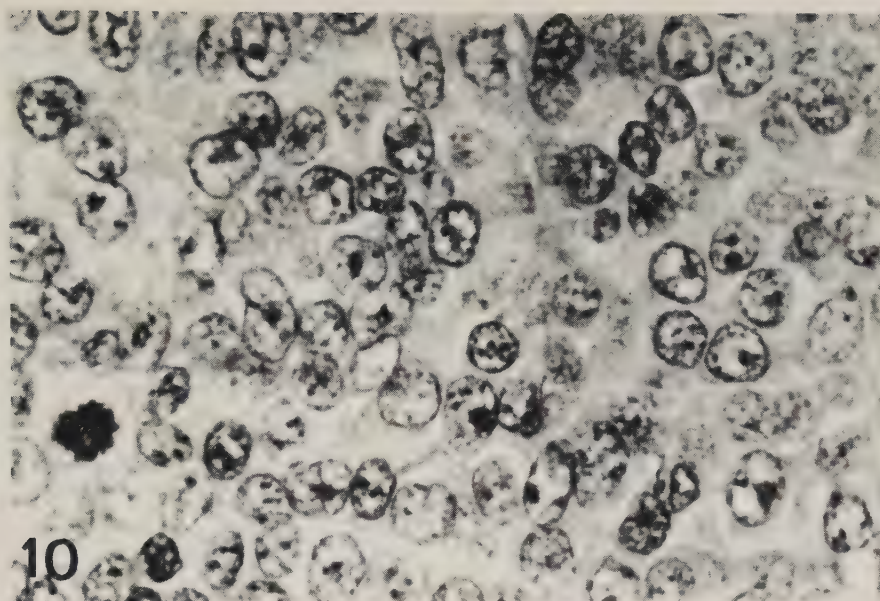


Fig. 12. LLD-2. Bone marrow aspirate dominated by prolymphocytes. Occasional mature lymphocyte. Case 663/58 .

Fig. 13. Blood picture of case 663/58, showing a cellular picture identical to that of the bone marrow and the lymph node (figs. 11 and 12).

Fig. 14. Necropsy specimen of vertebral bone marrow of case 663/58 (LLD-2), demonstrating fibrosis. van Gieson, x 300.

Fig. 15. Appearance of the lymph nodes in the necropsy specimens of case 663/58. Fibrosis similar to that of the bone marrow. x 450.

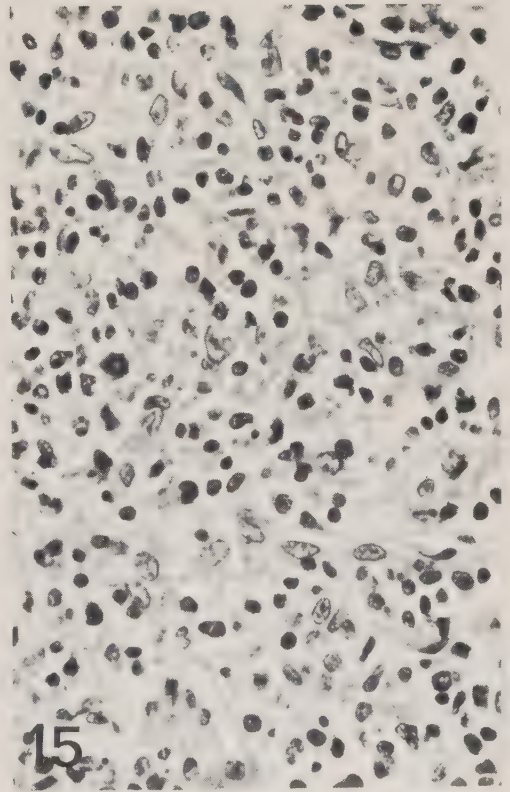
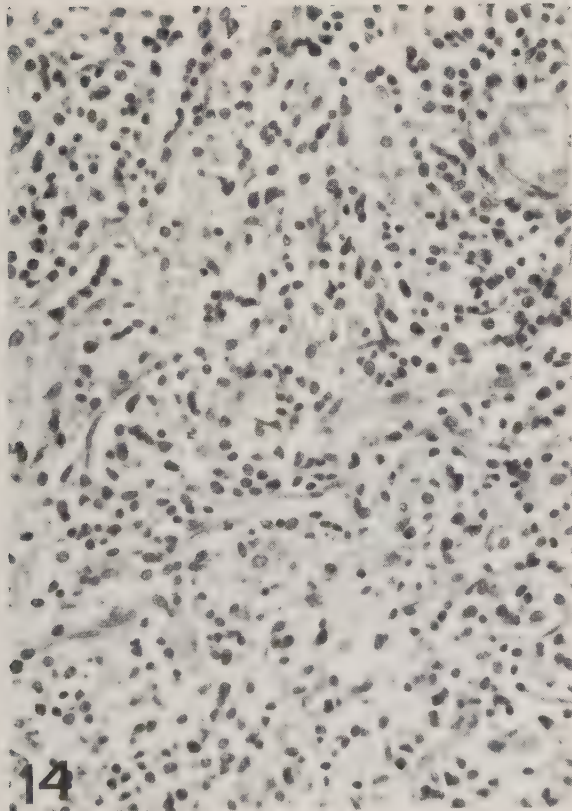
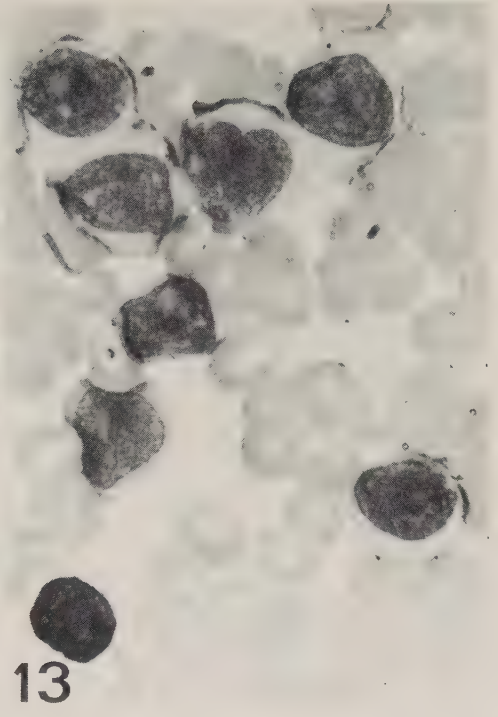
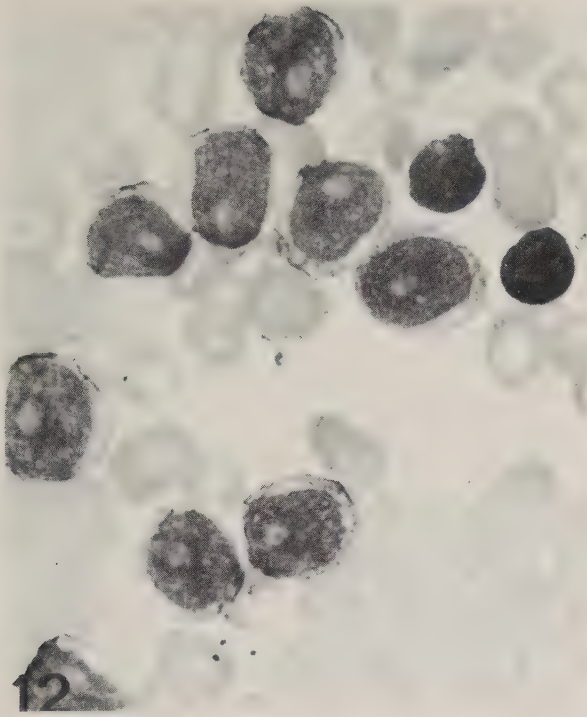


Fig. 16. Fibrosing portal infiltrate of the liver in case 663/58 (LLD-2). x 100.

Fig. 17. Cytologic bone marrow picture of case 671/66 (LLD-2). Many prolymphocytes and mature lymphocytes.

Fig. 18. Bone marrow group 2 (case 151/65) demonstrating prolymphocytes and occasional mature lymphocytes in bone marrow smear. Compare fig. 19.

Fig. 19. Blood picture of case 151/65 on same occasion, demonstrating only mature lymphocytes. Compare fig. 18.

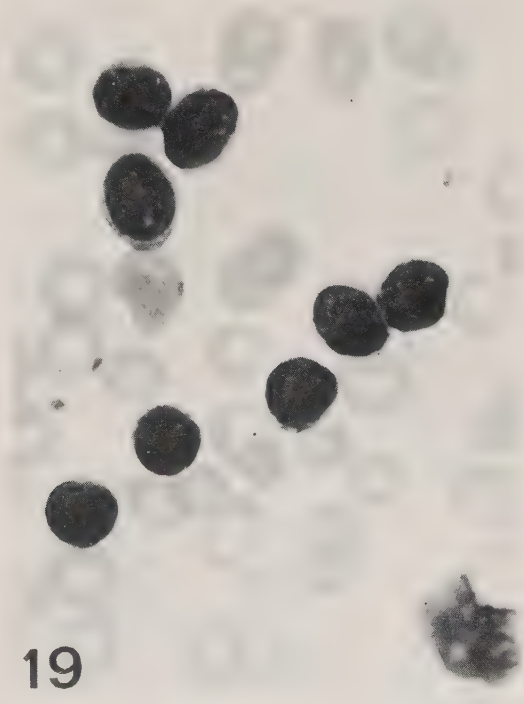
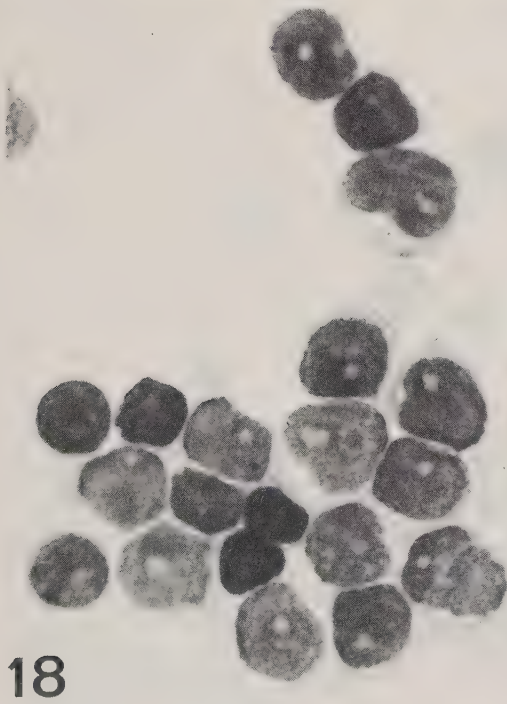
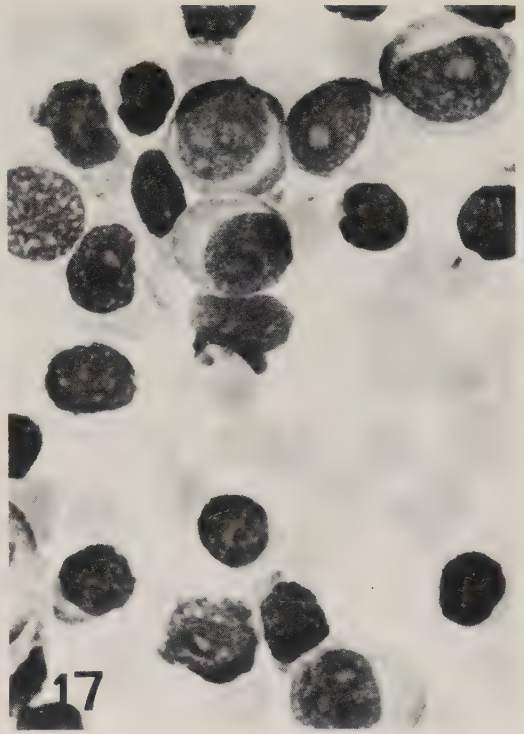


Fig. 20. LLD-3. Lymph node biopsy specimen from case 705/70. Somewhat atypical large immature cells and small, partly somewhat atypical lymphocytes. No IF. Giemsa, x 530.

Figs. 21, 22 and 23. LLD-3. Bone marrow smear from case 705/70, demonstrating atypical lymphocytes.

Figs. 24 and 25. Blood picture of case 705/70 (compare figs. 21-23). Atypical cells, some with cleaved nucleus.

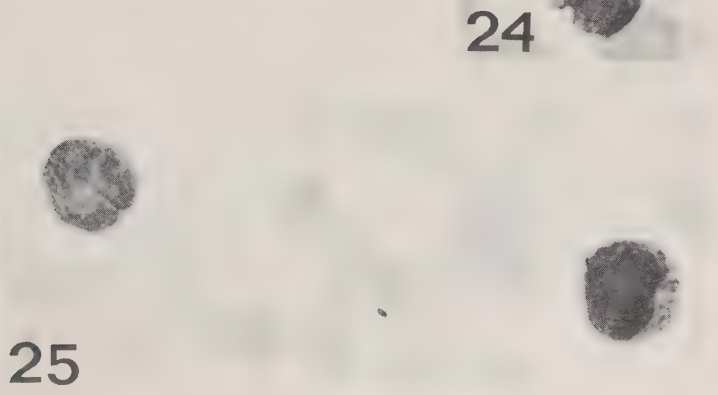
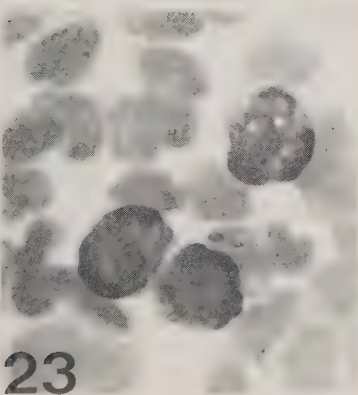
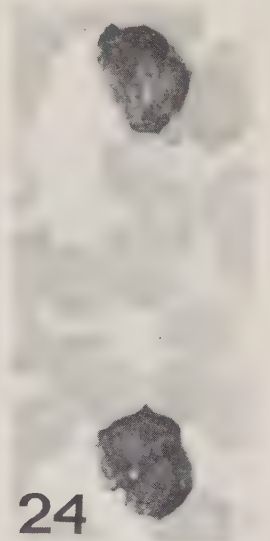
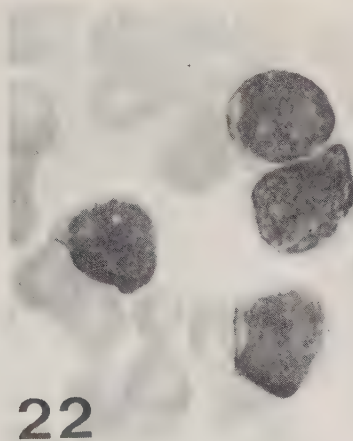
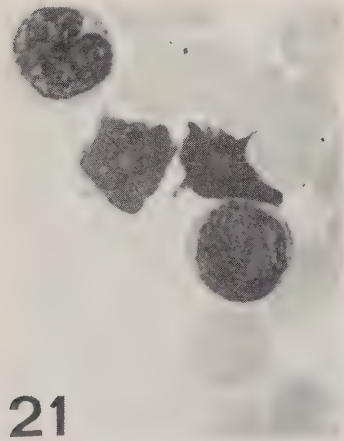
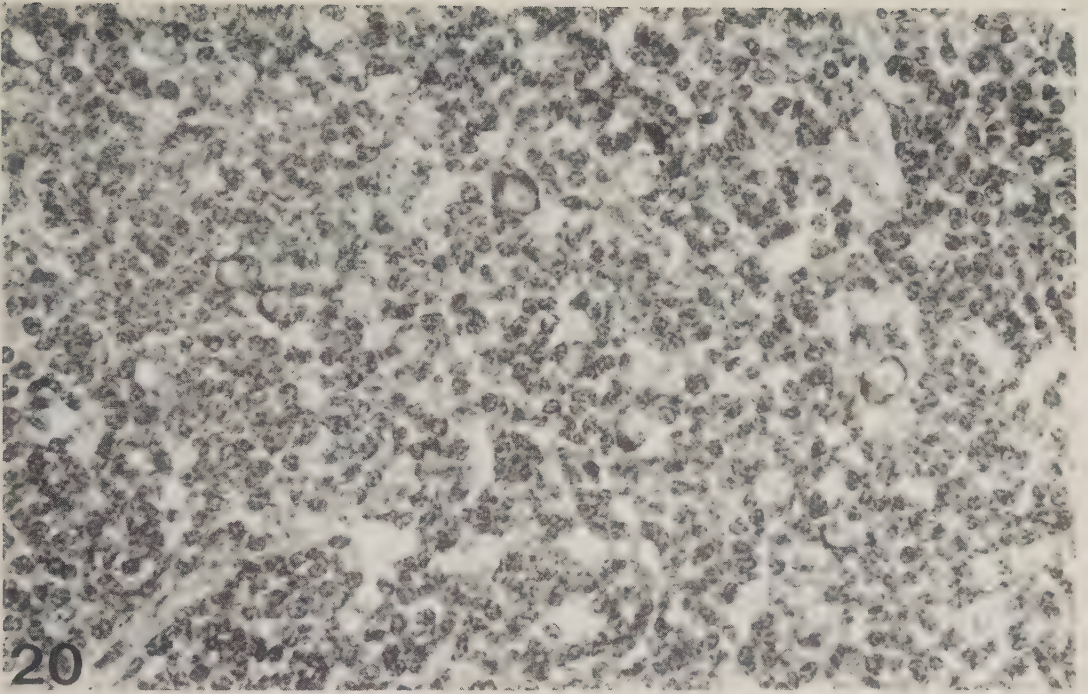


Fig. 26. LLD-3. Section of aspirated bone marrow particle from case 1147/65. Rather dense, but unevenly distributed infiltration of predominantly small and mature lymphocytes. x 450.

Fig. 27. Bone marrow smear from case 1147/65, demonstrating mature, atypical cells clustered around histiocytes.

Fig. 28. LLD-3. Electron micrograph from section prepared from same block as fig. 26. Note predominantly mature appearance of cells, but many with deep clefts and generally irregular shape of the nucleus. G = granulocytes. x 5700.

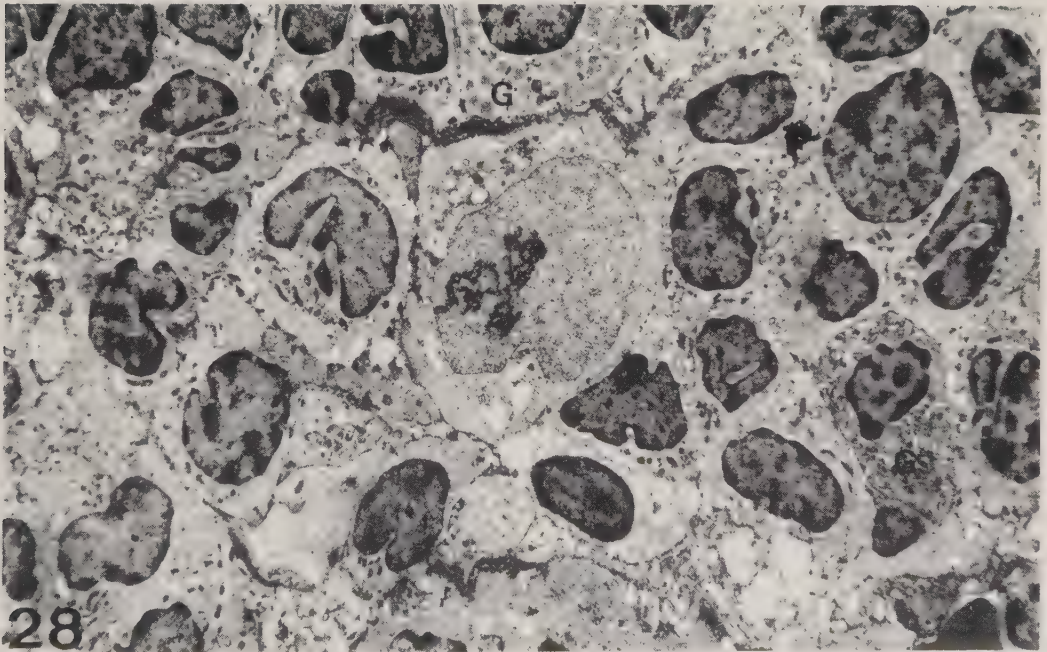
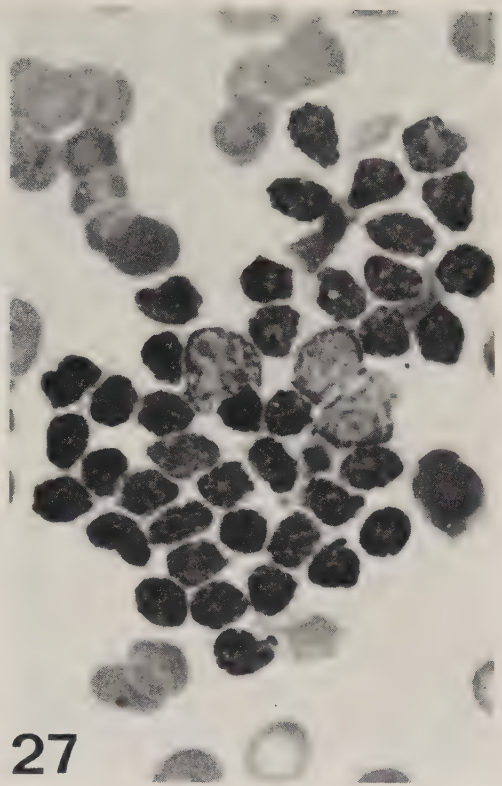
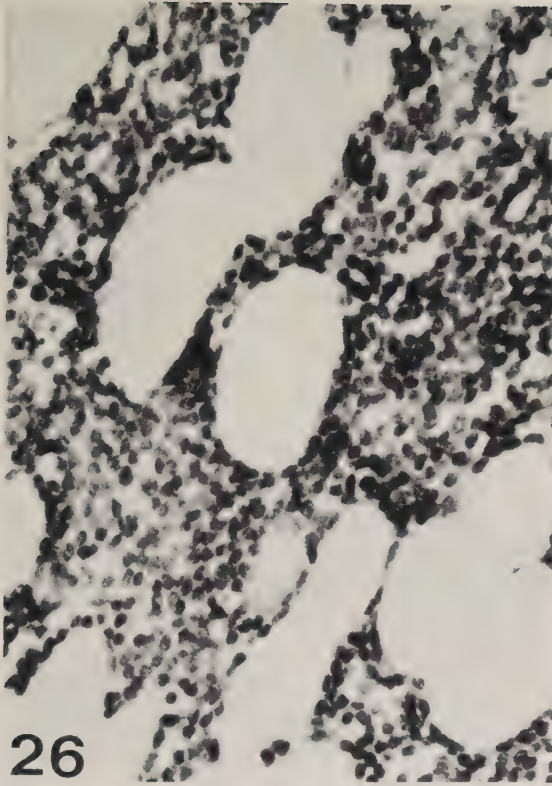


Fig. 29. LLD-3. Bone marrow smear of case 1140/71 demonstrating small group of atypical but predominantly mature lymphocytes.

Fig. 30. LLD-3. Lymph node biopsy specimen from case 1140/71, demonstrating large immature cell and partly atypical lymphocytes. x 1120.

Fig. 31. Necropsy specimen of lymph node from case 1140/71 (LLD-3), demonstrating lymphocytic infiltrates at the hilus of a lymph node with small focus of large-cell tumour with a slightly granulomatous appearance, resembling Hodgkin's disease. x 180.

Fig. 32. High magnification of the tissue resembling Hodgkin's disease of fig. 31. x 450.

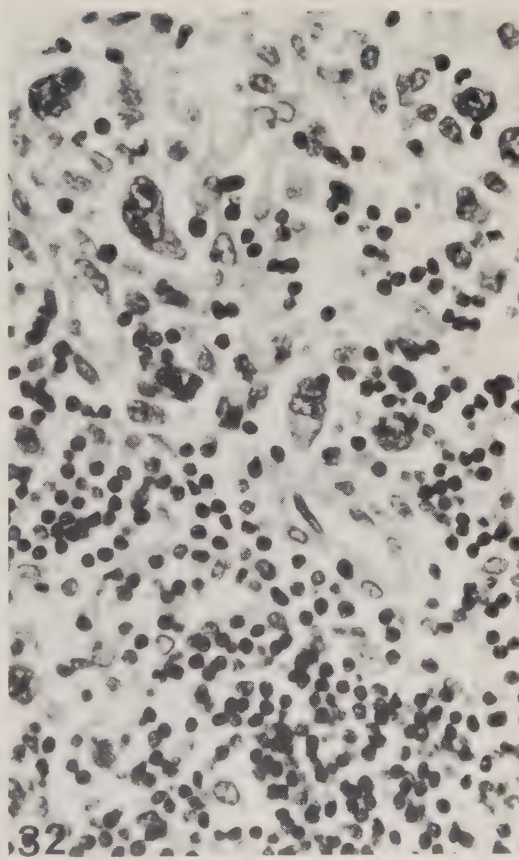
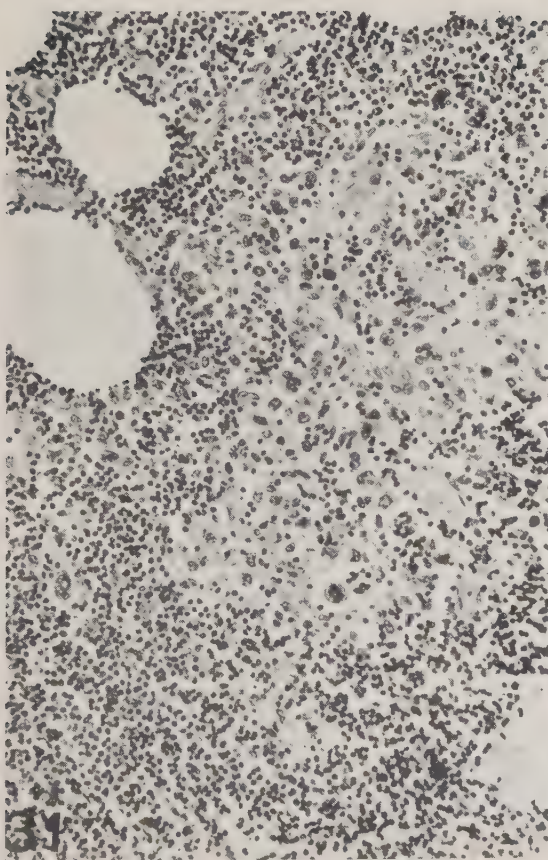
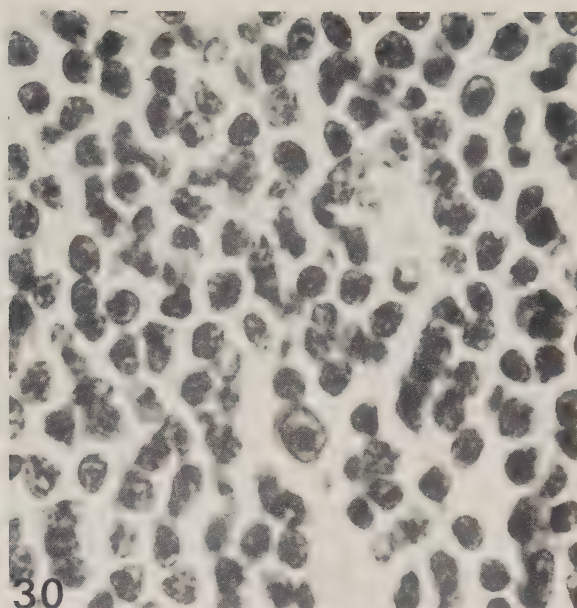


Fig. 33. LLD-3. Section of bone marrow particles from case 1120/60. Dense but uneven infiltration of lymphoma. x 55.

Fig. 34. Higher magnification of fig. 33. Atypical but predominantly mature lymphocytes. x 800.

Fig. 35. Smear of bone marrow aspirate from case 1120/60. Compare fig. 34.

Fig. 36. Atypical cells in the peripheral blood from case 1120/60.

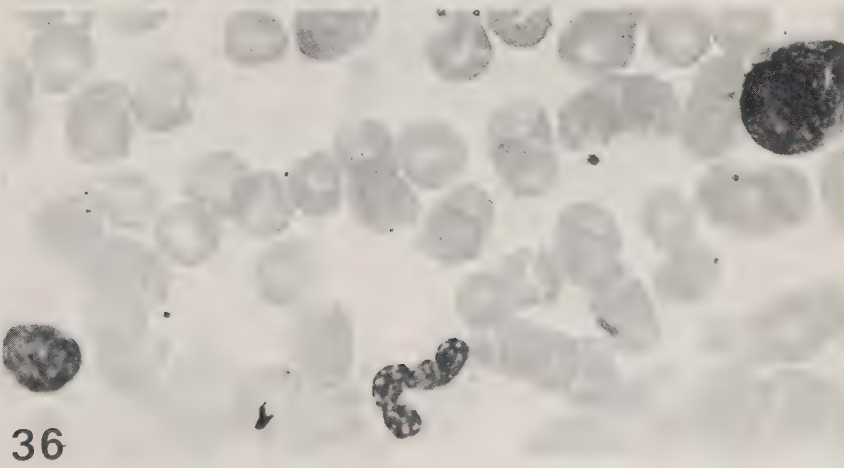
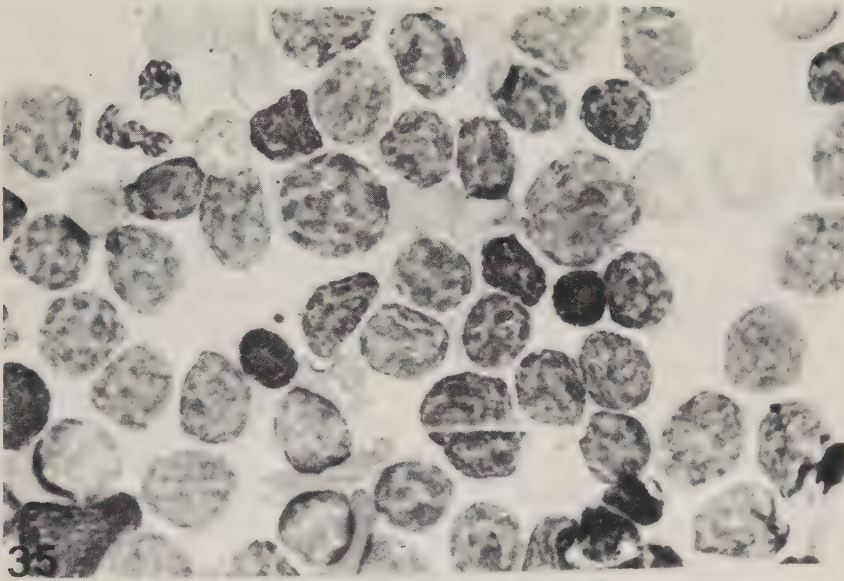
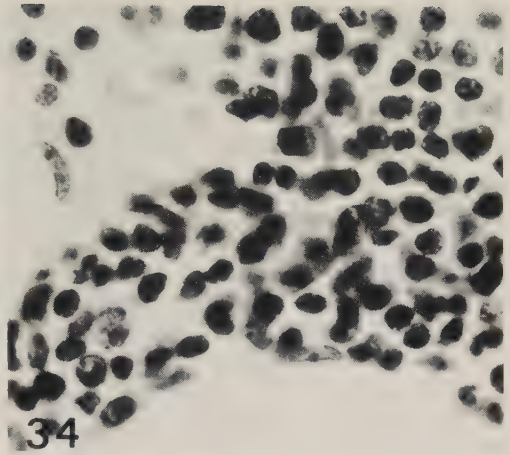
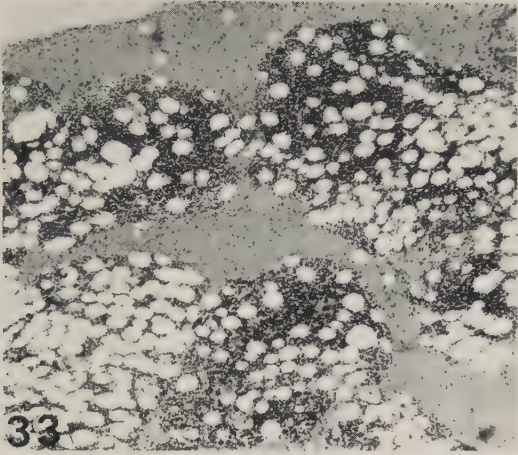


Fig. 37. Lymph node biopsy specimen of case 1120/60 (LLD-3), demonstrating large immature cells and both atypical and apparently normal lymphocytes. x 1120.

Fig. 38. Appearance of a lymph node in the necropsy specimens of case 1120/60, demonstrating HL. Compare fig. 37. x 1120.

Fig. 39. LLD-3. Splenic aspirate from case 220/72. Lymphocytic cells of varying atypia and maturity.

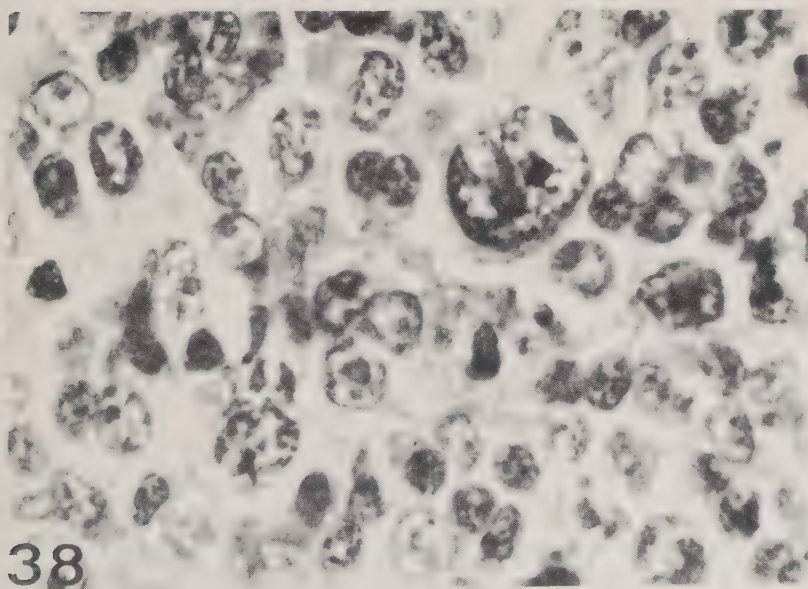
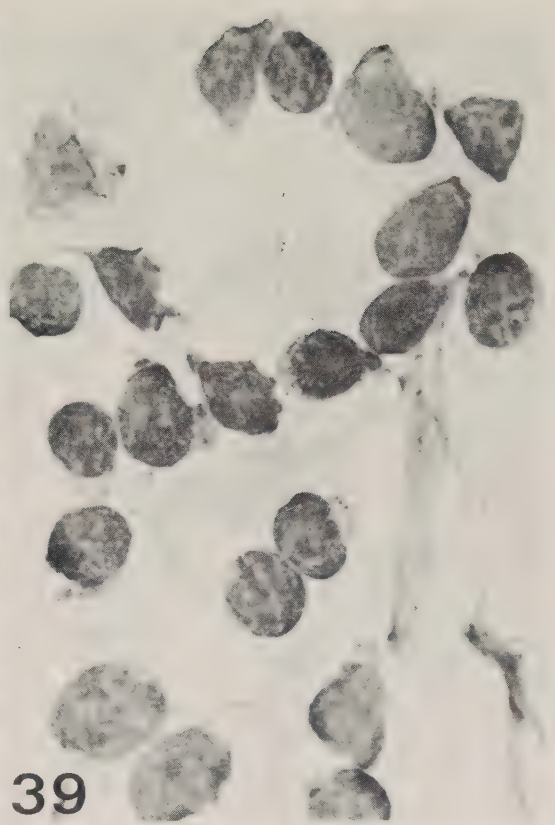
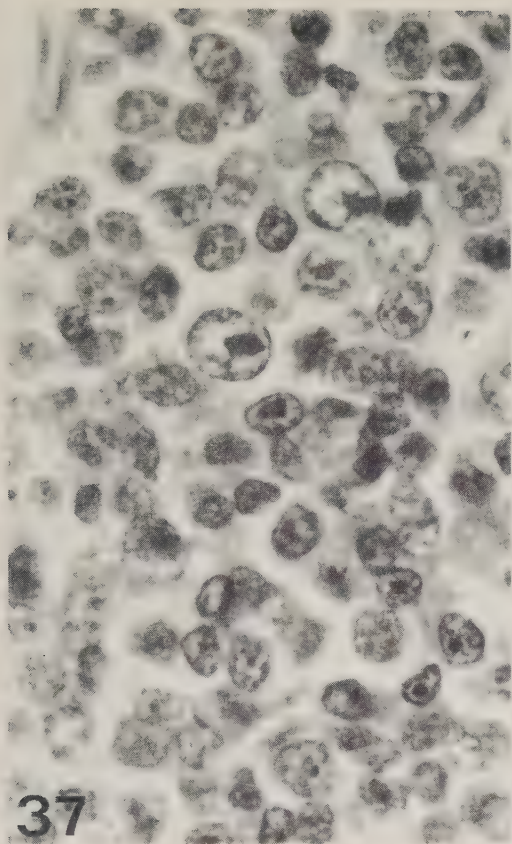


Fig. 40. LLD-4. Section of lymph node biopsy specimen of case 451/61. Possibly faint tendency to formation of a follicle in lower part of illustration. No large immature cells similar to those of LLD-1, -2 or -3. x 450.

Fig. 41. High power view of fig. 40, demonstrating irregular shape of cells and very few apparently normal lymphocytes. One large immature cell. x 1120.

Fig. 42. Same lymph node as figs. 40 and 41 stained with methyl-green and pyronin. Note many intensely stained plasma cells (indicated by arrows). Occasional blast cells (asterisks). x 1120.

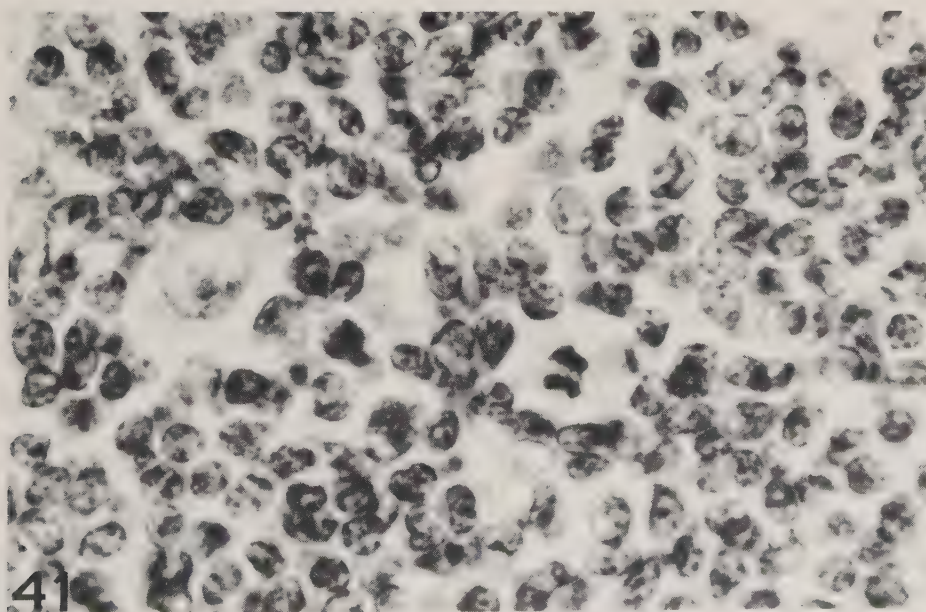
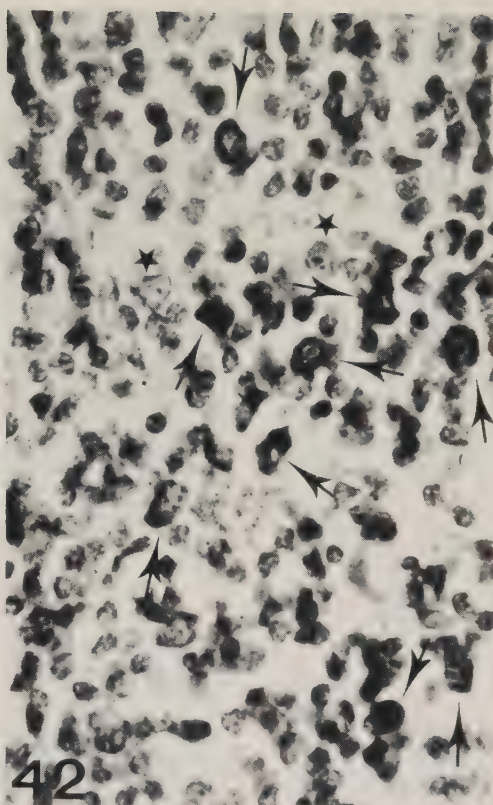
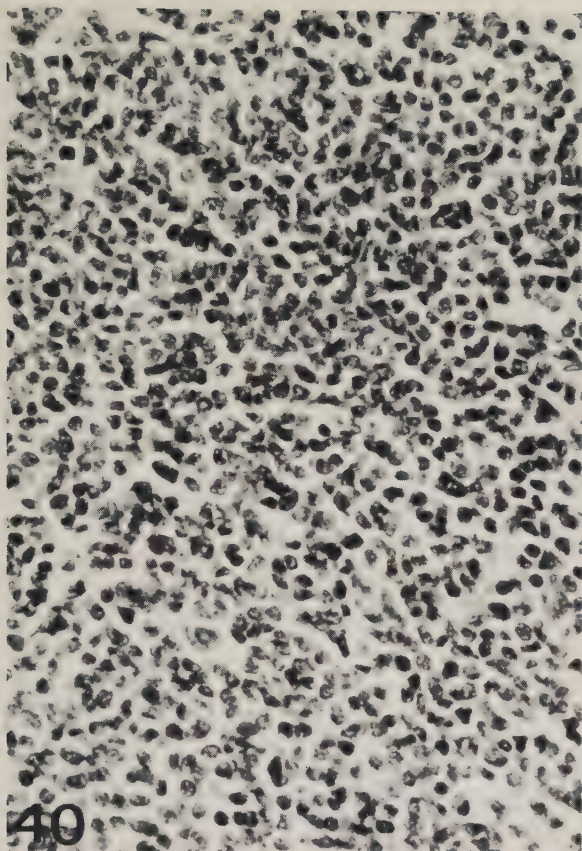
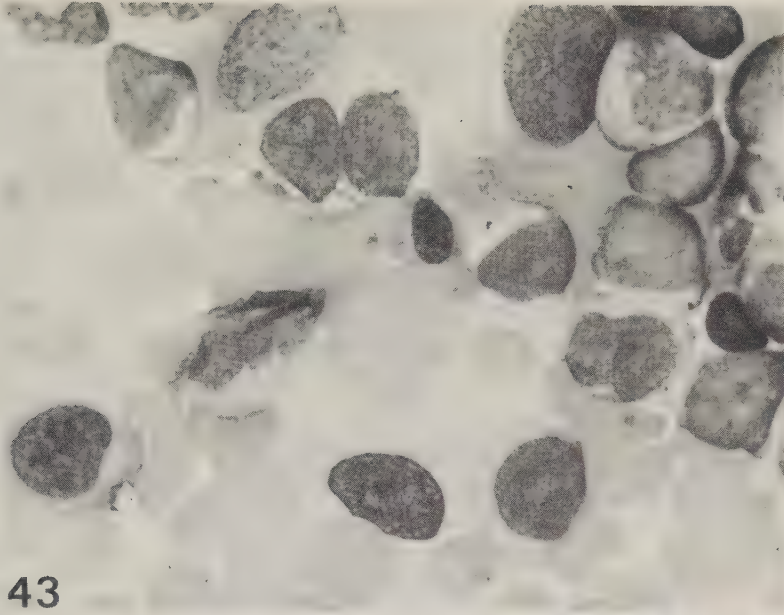


Fig. 43. Bone marrow smear from case 451/61. Some cells with irregular-shaped nuclei, but nuclear contour often rounded or oblong. Nucleolus variably visible.

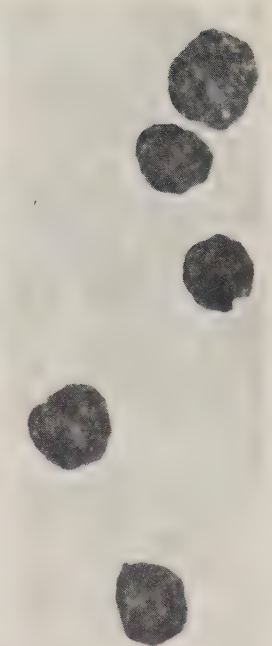
Fig. 44. LLD-4. Peripheral blood from case 619/64. Atypical nuclei but preponderantly mature structure. Many of the cells have a "notched" appearance. This type of cell is not specific of nodular lymphomas but occurs also in LLD-4.

Figs. 45 and 46. LLD-4. Bone marrow smear from case 963/66. Irregular, generally somewhat immature nuclei with varying visibility of nucleolus.

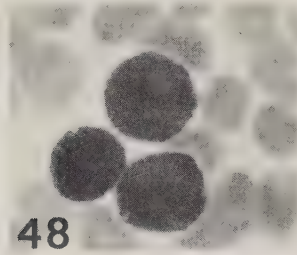
Figs. 47 and 48. LLD-4. Blood picture of case 963/66. Cells are essentially similar to those in bone marrow (figs. 45 and 46).



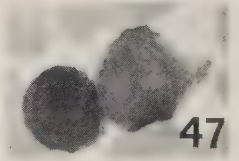
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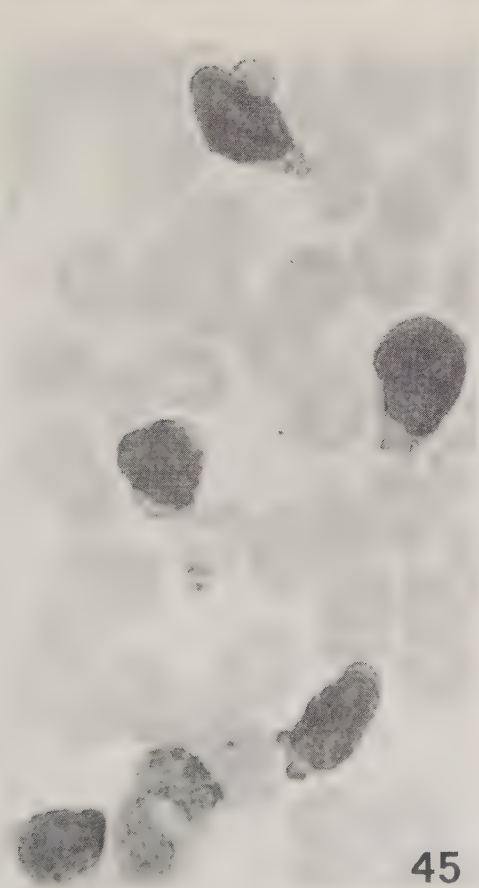
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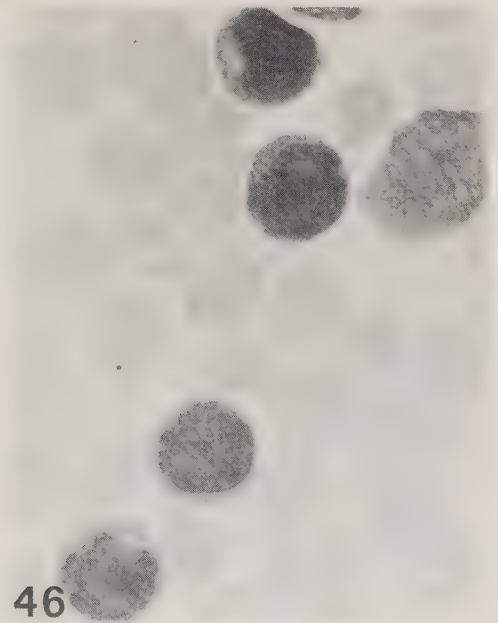
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Fig. 49. LLD-4. Lymph node biopsy specimen from case 535/62. Slight "cloudiness" faintly resembling nodularity, but no well-formed follicles. In low magnification the picture may be mistaken for IF, but readily recognized by high power scrutiny. x 75.

Fig. 50. Lymph node aspirate from LLD-4 (865/67). Blast cells (arrow) and lymphocytes with varying maturity and atypia.

Fig. 51. LLD-4 of large cell type (case 1047/63). Mitotic figure in centre. x 450.

Fig. 52. High power view of field in fig. 51. Atypical lymphocytes and occasional blasts (arrow). x 1120.

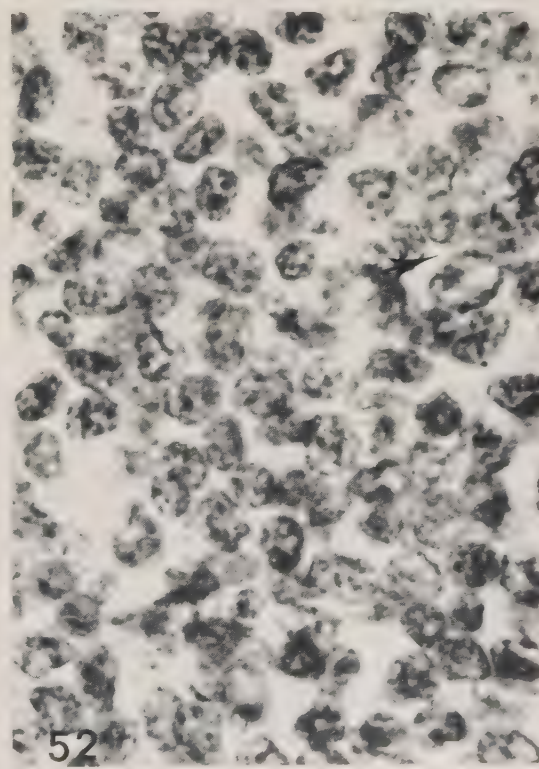
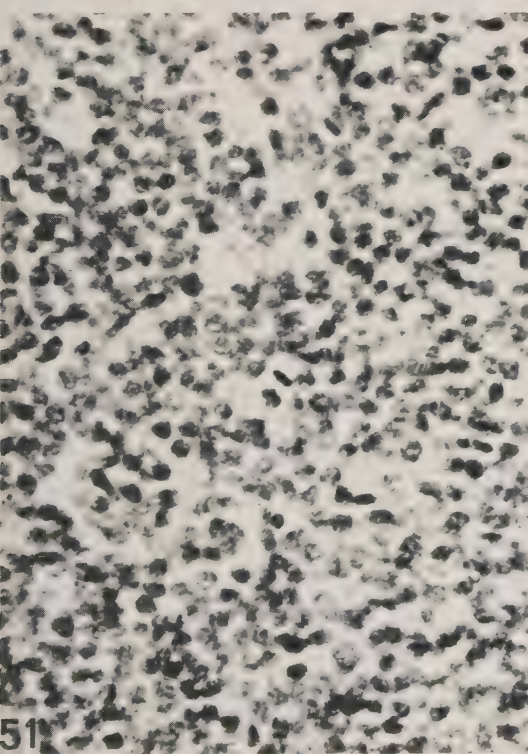
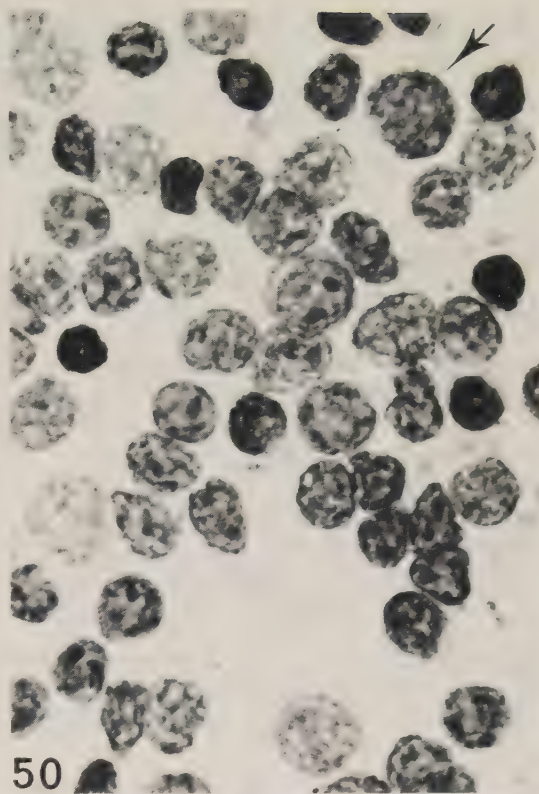


Fig. 53. LLN. Lymph node biopsy specimen from case 300/65. Many well-formed, follicle-like structures. Towards bottom of illustration a field of more diffuse tumour growth. x 30.

Fig. 54. LLN. High magnification of a follicle in fig. 53. Atypical lymphocytes and few blasts. x 1120.

Fig. 55. LLN. Lymph node biopsy specimen from case 219/73. Field with many blasts (arrows). Mitotic figure in blast (centre). x 1120.

Fig. 56. LLN. Aspirate from the node illustrated in fig. 55.

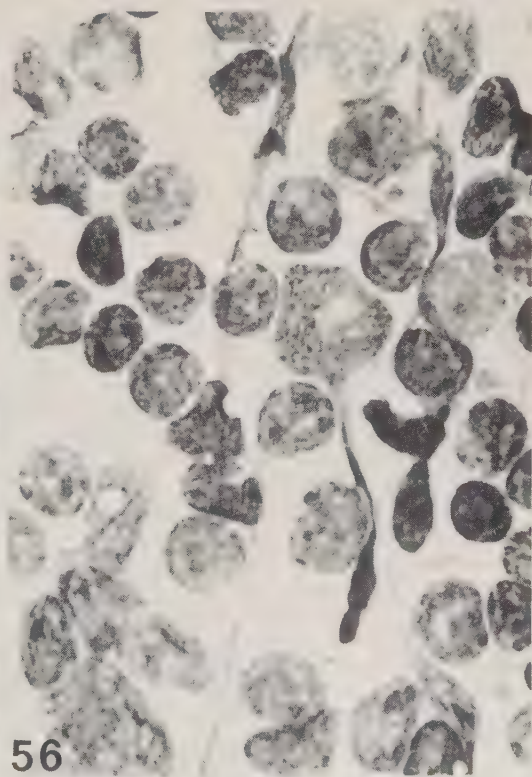
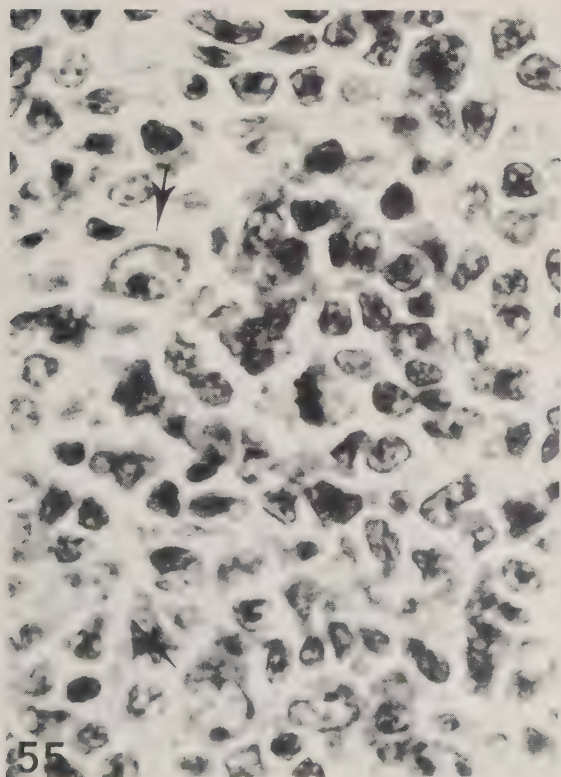
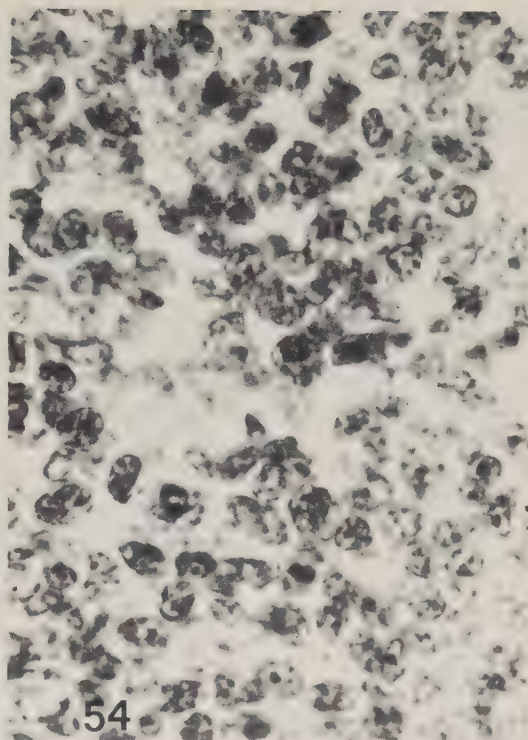
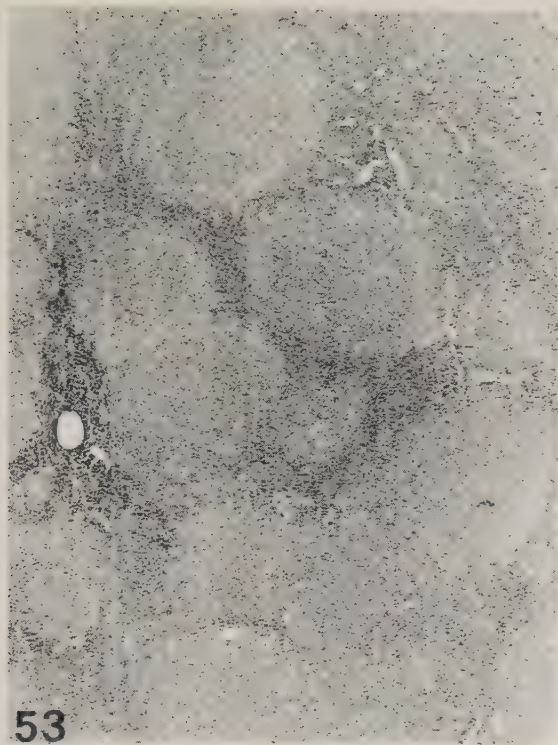


Fig. 57. LLN with transition to LLD-4. Lymph node biopsy specimen from case 341/71 . x 70.

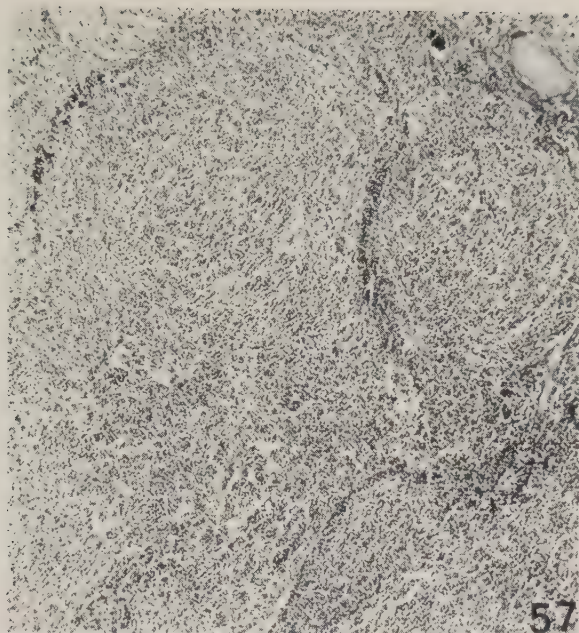
Fig. 58. LLN. Higher magnification of fig. 57. Especially in diffuse parts blast cells may be very few and atypia of the lymphocytes need not be striking. x 1120.

Fig. 59. LLN. Blood picture in case 300/65, demonstrating small and predominantly mature cells, but with atypical ("notched") nuclei. A nucleolus occasionally discernible.

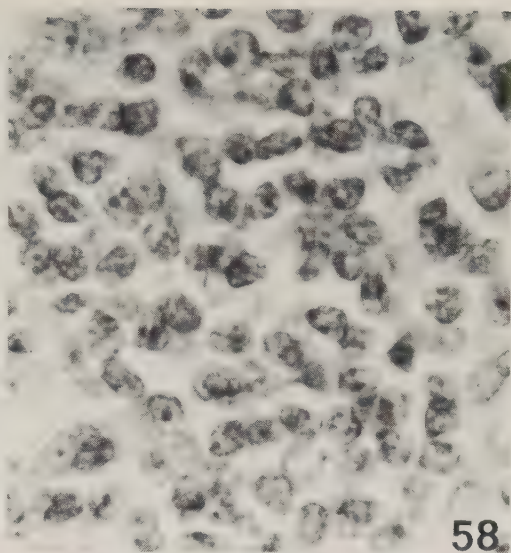
Figs. 60 - 63. LLN. Cells from bone marrow smear of case 219/73. "Notched" cells in figs. 62 and 63, but immature cells also present.

Fig. 64. LLD-4. Bone marrow smear from case 397/59 demonstrating group of rather undifferentiated tumour cells similar to blastic leukemia. Cells with a lymphocytic character are also seen.

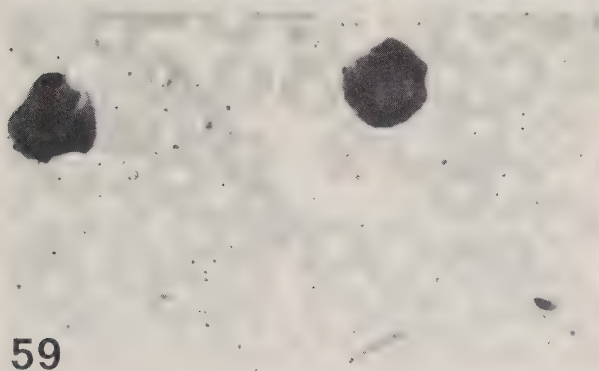
Fig. 65. Blood picture in case 397/59 (compare fig. 64). Apparently mature, but atypical cells.



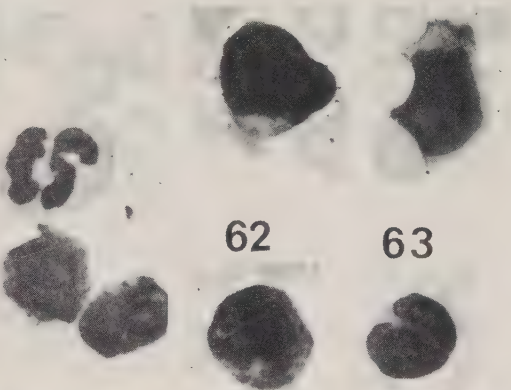
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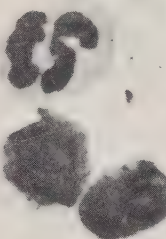


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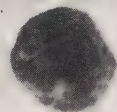
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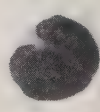


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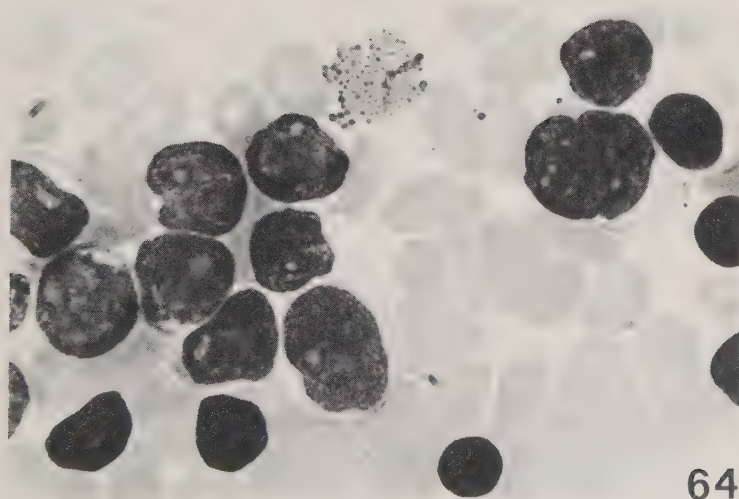


Fig. 66. LLN. Bone marrow smear of case 799/73, demonstrating "diplococcoid" cells. The cell to the right has immature features.

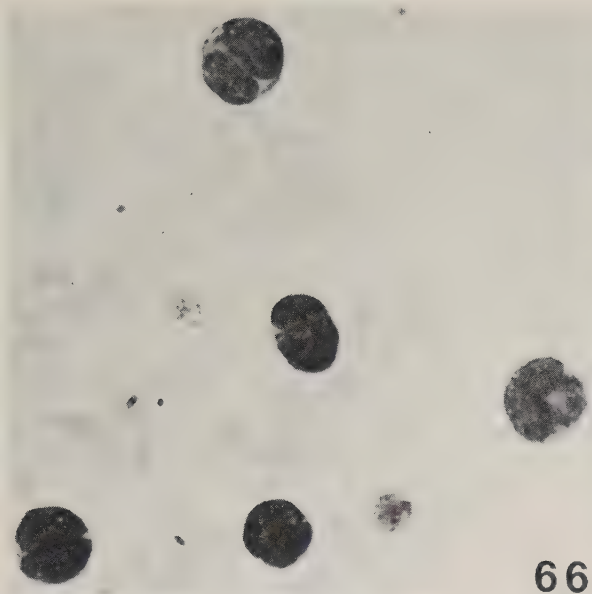
Fig. 67. Blood picture in case 799/73. Compare figs. 66 and 70. Except for the double nucleus the appearance of the lymphocyte is not strikingly abnormal.

Fig. 68. Lymph node of case 799/73, demonstrating LLN with transition to HL. x 30.

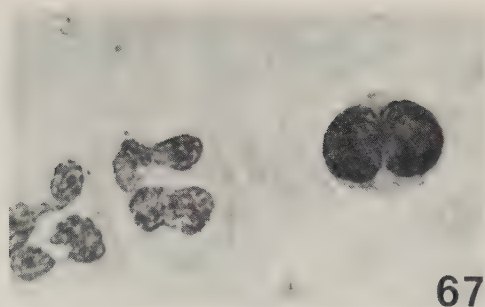
Fig. 69. LLN. Case 799/73. A tumour nodule. Pronounced autolysis, but still many cells with double nuclei are visible. Some of the blast cells also appear to have double nuclei (arrows). x 1120.

Fig. 70. Extra-nodular lymphomatous parenchyma of the same node as fig. 69. Many small, mature, "diplococcoid" cells. x 1120.

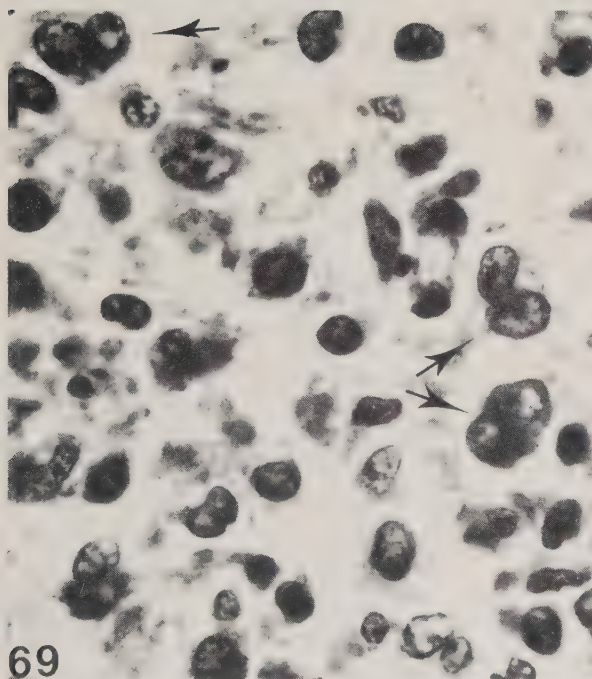
Fig. 71. HL-cells with double nuclei from focus in fig. 68. x 1120.



66



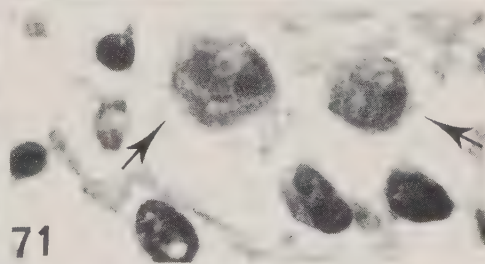
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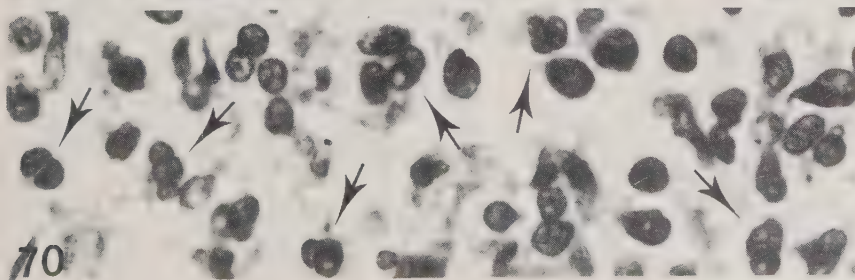
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70

Fig. 72. Blood smear from case 437/67 (bone marrow group 1-3). Many irregular nuclei.

Fig. 73. Bone marrow smear from case 437/67 (bone marrow group 1-3). Atypical cells, some with discernible nucleoli.

Fig. 74. Fine needle aspirate of pharyngeal tumour (HL) of case 437/67. Many hyaline inclusions in the cytoplasm.

Fig. 75. Histologic section of biopsy from pharyngeal tumour (HL) in case 437/67. Tumour cells have giant nucleoli. Some hyaline inclusions (arrows). Epithelium in upper right corner. Toluidine blue, x 1120.

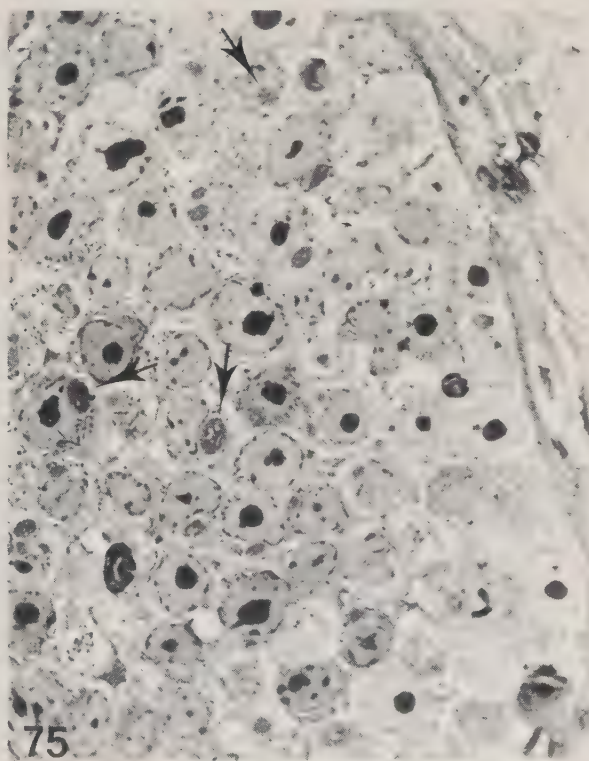
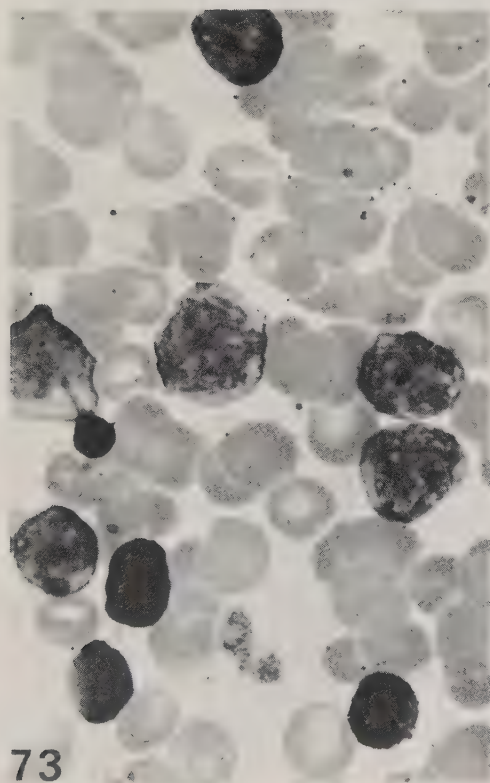
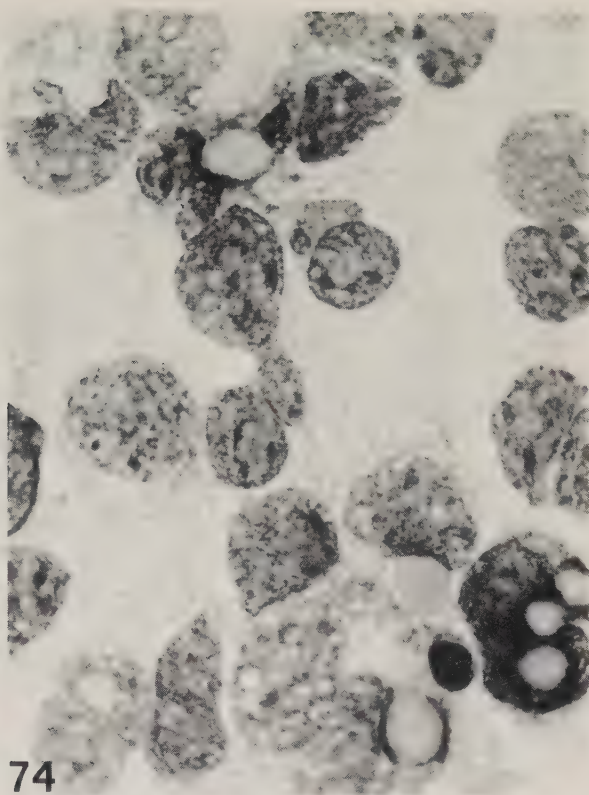
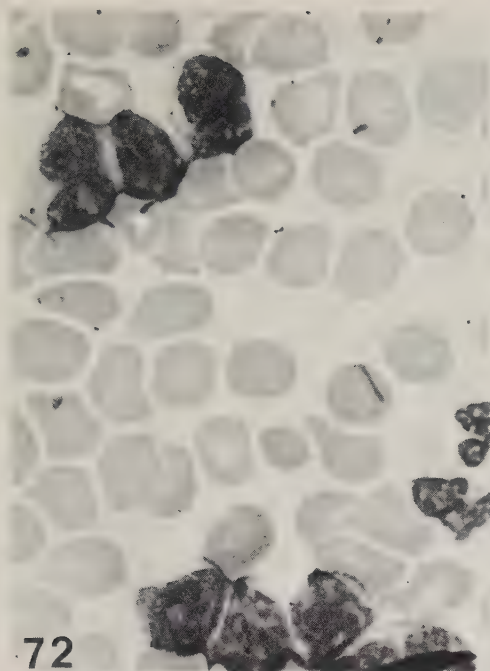


Fig. 76. Electron micrograph of pharyngeal tumour of case 437/67 (compare fig. 75). Light and dark cells. Hyaline inclusions in cytoplasm of some light cells (arrows). x 4500.

Fig. 77. Electron micrograph of a dark cell of pharyngeal tumour, case 437/67. The cell has a huge nucleolus. Cytoplasm shows many profiles of granular endoplasmic reticulum. The cell has plasmacytoid features. x 6000.

Fig. 78. Higher magnification of granular endoplasmic reticulum of a dark cell in HL-tumour in case 437/67. In some places electron dense material is accumulated within the granular endoplasmic reticulum, similar to what may be seen in plasma cells. x 17000.

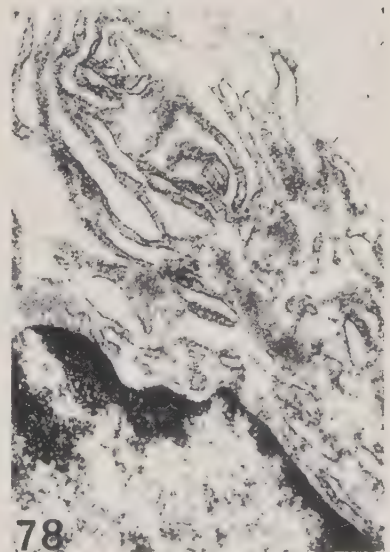
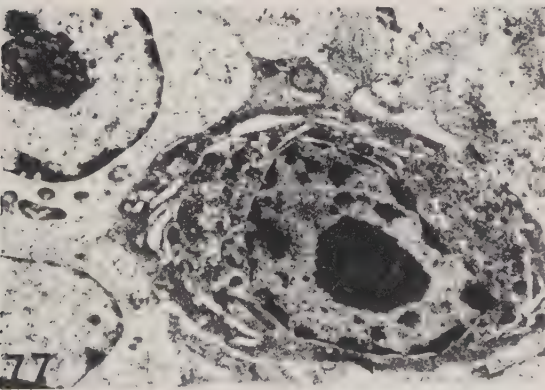
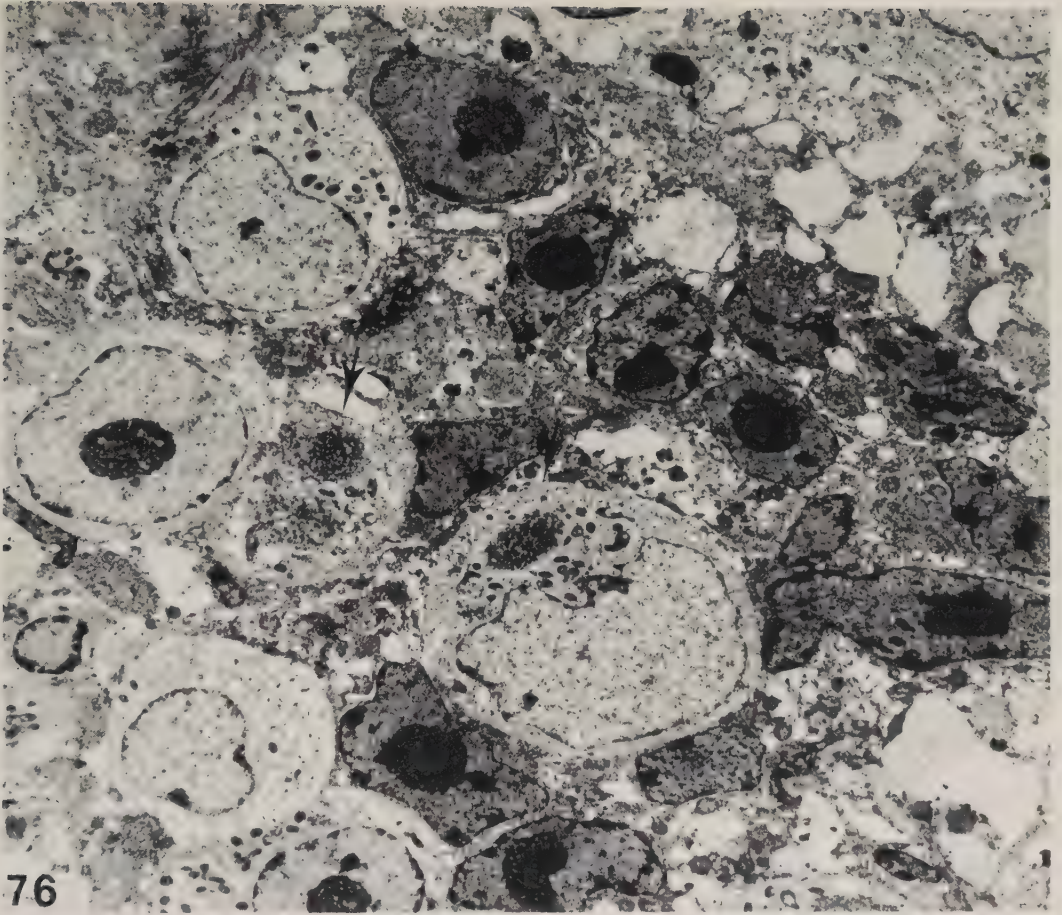
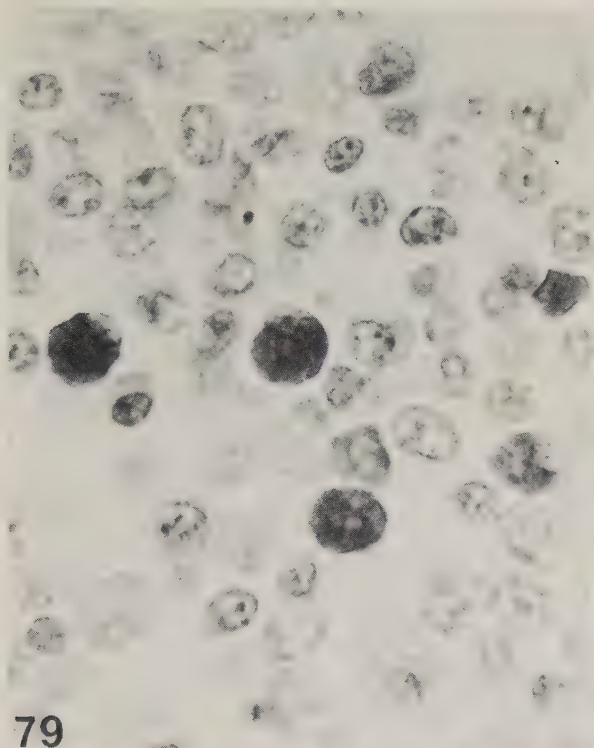


Fig. 79. Necropsy specimen of pharyngeal tumour from case 437/67. Many PAS-positive hyaline inclusions in tumour cells. Nucleus often pushed to periphery. Cell with phagocytosis (lower centre). This cell is probably a reactive macrophage. PAS, x 1120.

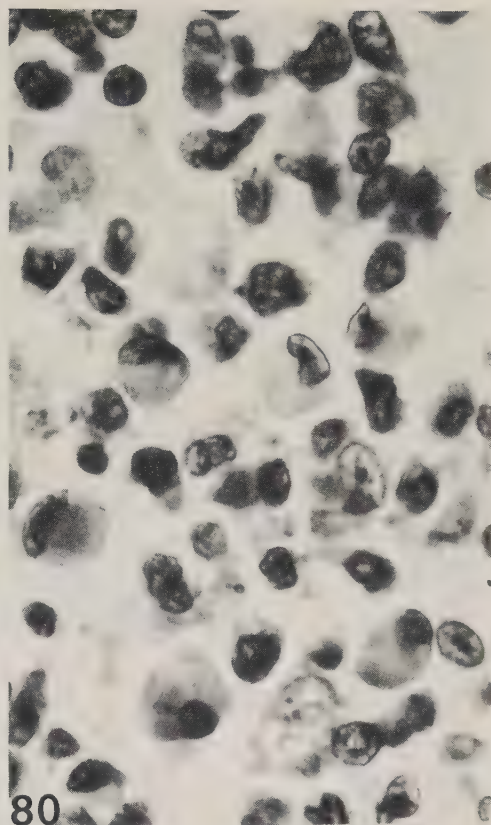
Fig. 80. Same tissue as in fig. 79, stained according to Ladewig. In some cells the hyaline inclusions stain red (low centre), in others the inclusions stain light bluish (upper right). The cell in the lower right part of the reproduction contains both red and bluish inclusions. Ladewig, x 1120.

Fig. 81. Bone marrow smear from case 913/72 (bone marrow group 1-3). All the cells are atypical and a nucleolus is discernible in most of them. Still, two generations seem to be recognizable and the cell in the upper left part of the picture resembles a prolymphocyte.

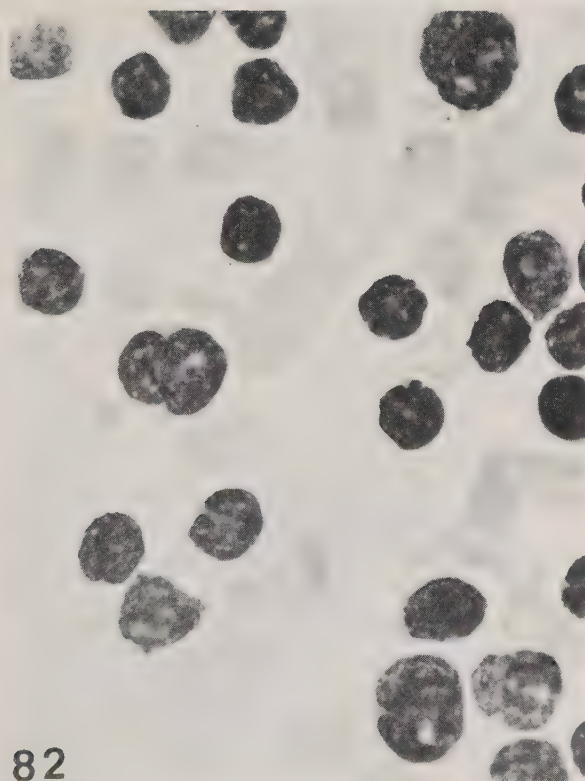
Fig. 82. Bone marrow smear from case 109/67 (bone marrow group 1-3). Generally irregular and atypical cells, but few with immature features. Especially the larger cells have cleft nuclei.



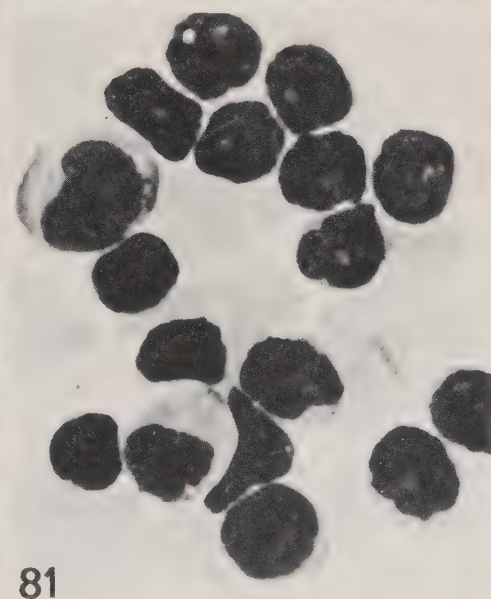
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Fig. 83. Bone marrow smear from a case of Waldenström's macroglobulinemia (820/70). A group of cells with a histiocyte, lymphocytes, plasma cells, and "lymphoplasmacytoid" cells with intermediate morphology. Note angular plasma cells.

Fig. 84. Another group of cells in a bone marrow smear of case 820/70, similar to that in fig. 83. Note vacuole in cytoplasm of cell in the centre.

Fig. 85. Plasma cells in bone marrow smear of case 820/70 (macroglobulinemia) with intranuclear "vacuole". Sometimes it is possible to see the "vacuole" opening into the perinuclear space, and it is really an invagination into the nucleus (fig. 85 B).

Fig. 86. Histologic section of bone marrow in Waldenström's macroglobulinemia (case 1224/70). Moderately dense infiltration with lymphocytes and plasmacytoid cells. PAS-positive intracytoplasmic inclusions (arrow). PAS, x 370.

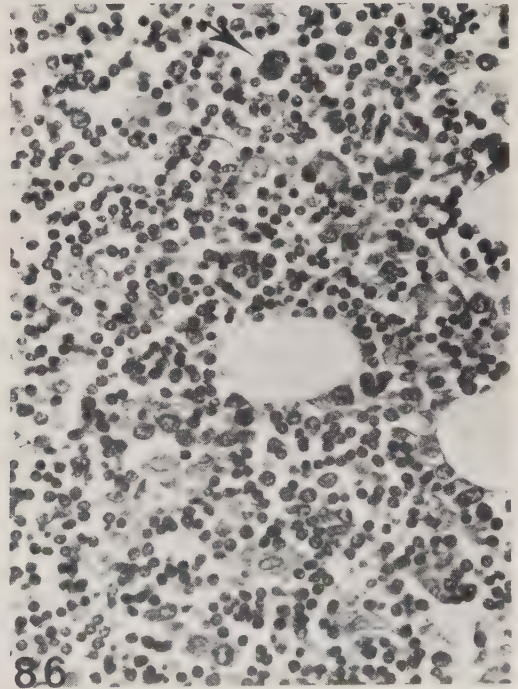
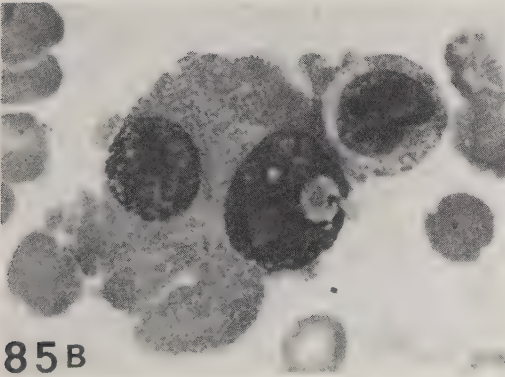
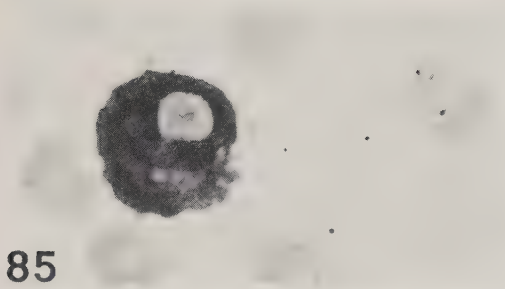
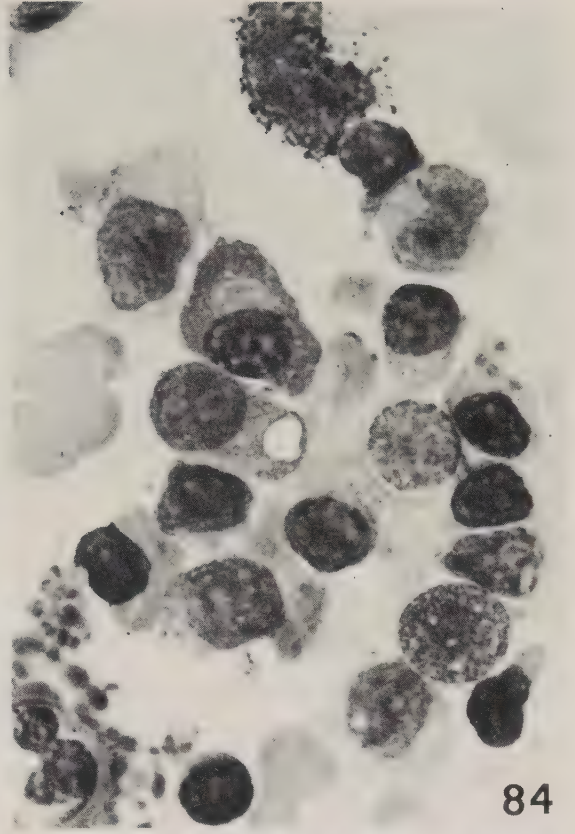
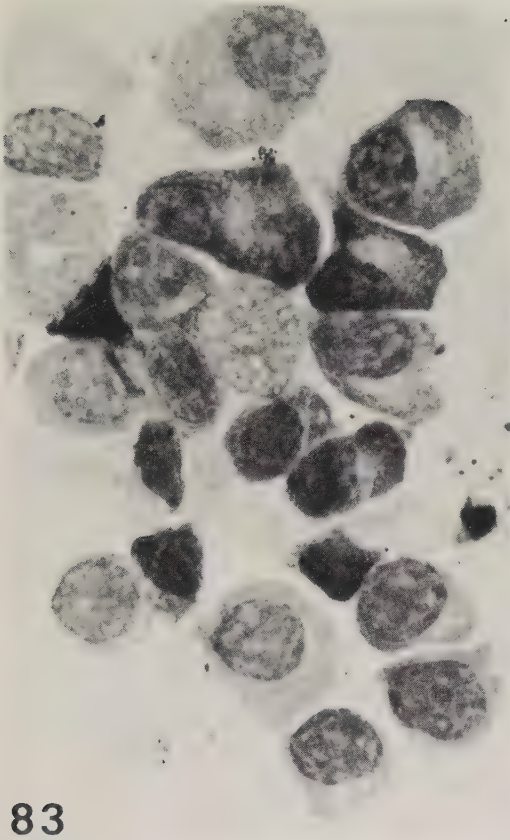


Fig. 87. Lymph node from case of Waldenström's macroglobulinemia (1224/70). Diffusely outlined fields of fairly large, plasmacytoid cells (right centre) and smaller, lymphocytic cells. x 220.

Fig. 88. Lymph node in Waldenström's macroglobulinemia (case 1224/70). Mature lymphocytes and some immature cells with irregular nuclei. x 1120.

Fig. 89. Dense infiltration of perinodal adipose tissue in Waldenström's macroglobulinemia (case 225/61). Lobular architecture of the adipose tissue is accentuated. x 40.

Fig. 90. Waldenström's macroglobulinemia. Another field of perinodal fat tissue from case 225/61, showing accentuated lobulation of infiltrated tissue due to pronounced dilatation of lymphatic vessels. x 40.

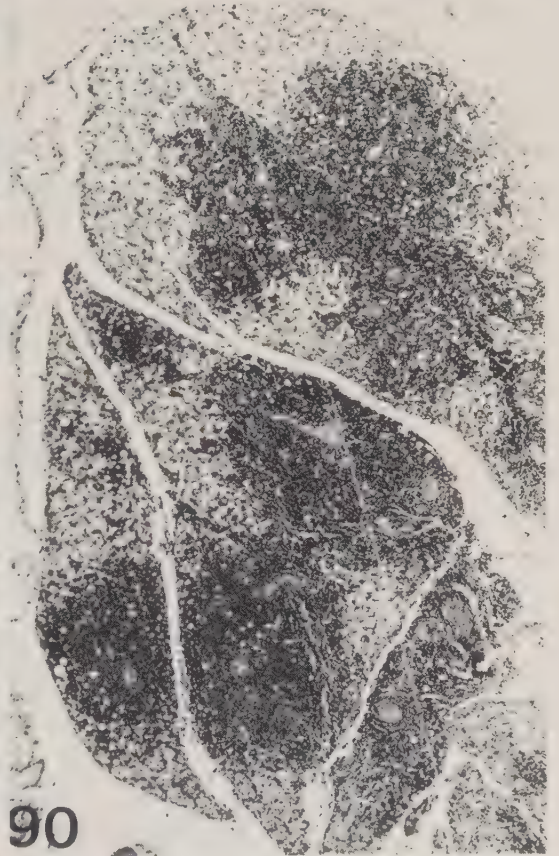
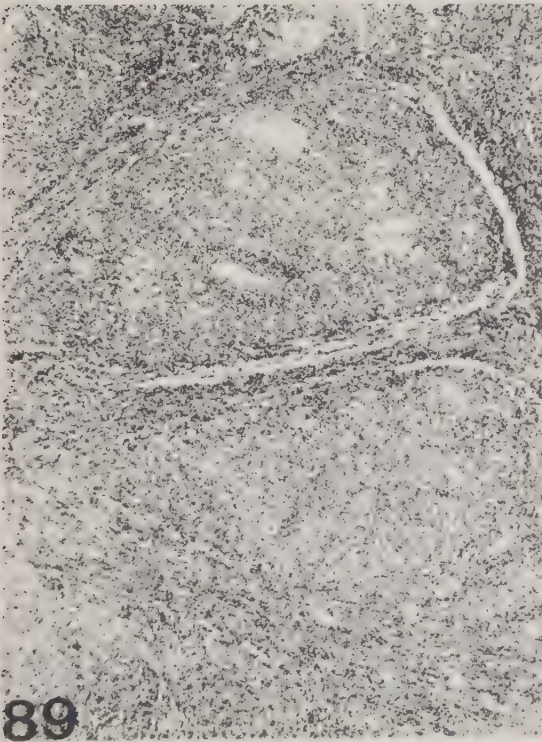
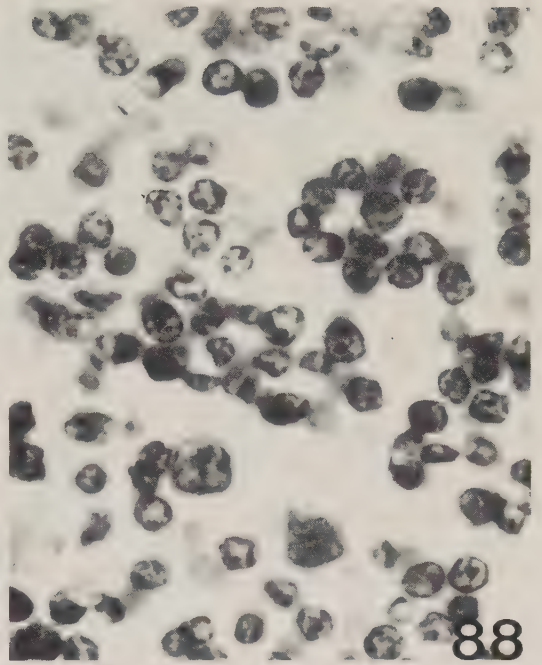


Fig. 91. Lymph node biopsy specimen from case 1224/70 (Waldenström's macroglobulinemia). Immature cells, similar to IF-cells of LLD-1. Mitotic figure in cell to the right. x 1120.

Figs. 92 and 93. HL-tumour of the spleen in case 1224/70. Many immature cells similar to those of the diffuse proliferation (compare fig. 91). Bizarre tumour cell in fig. 93. Many mitotic figures (arrows). Giemsa, x 1120.

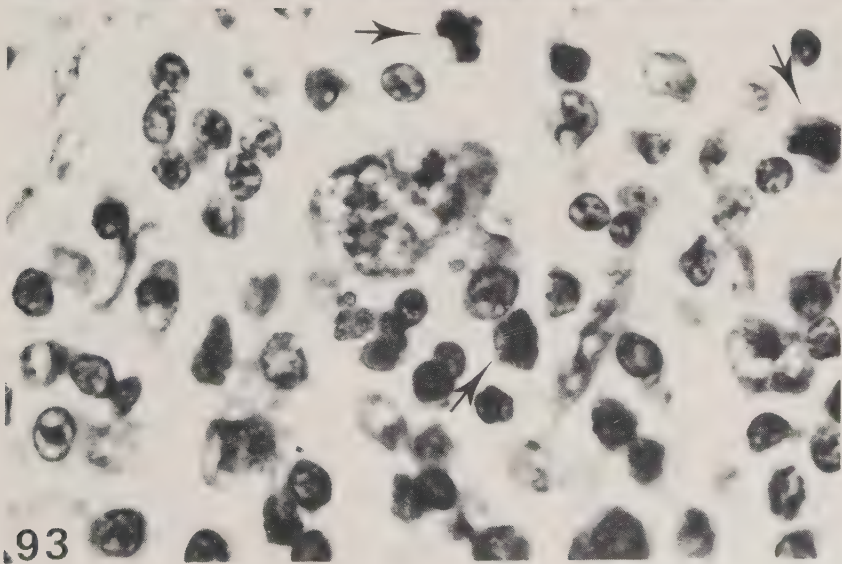
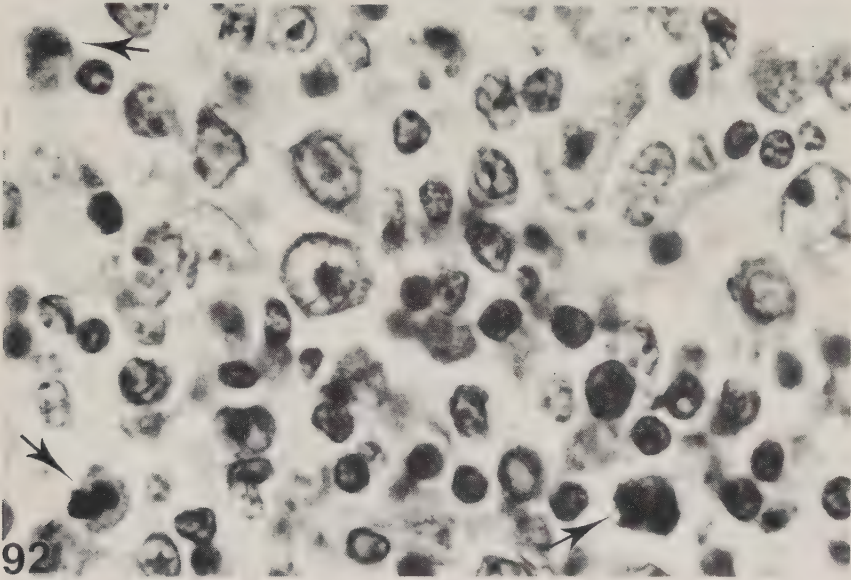
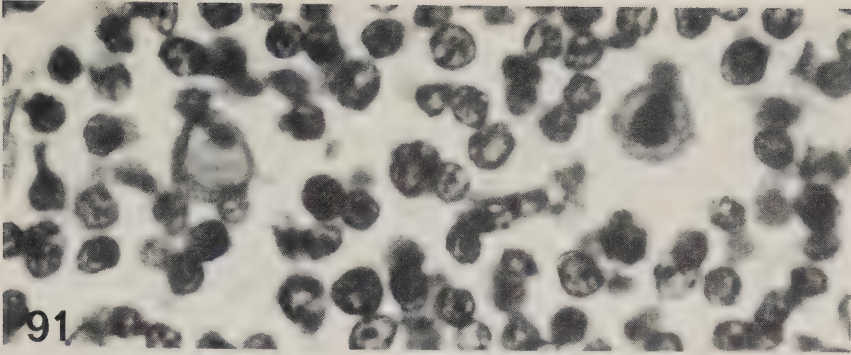


Fig. 94. Bone marrow infiltrates in case V.434/71 (Waldenström's macroglobulinemia). In the centre of the focus small lymphocytic cells (upper right) surrounded by a brim of larger plasmacytic cells. x 220.

Fig. 95. Lung tumour from case V.434/71. Diffusely outlined fields of small, lymphocytic cells (left) and larger, plasmacytoid forms (right). x 220.

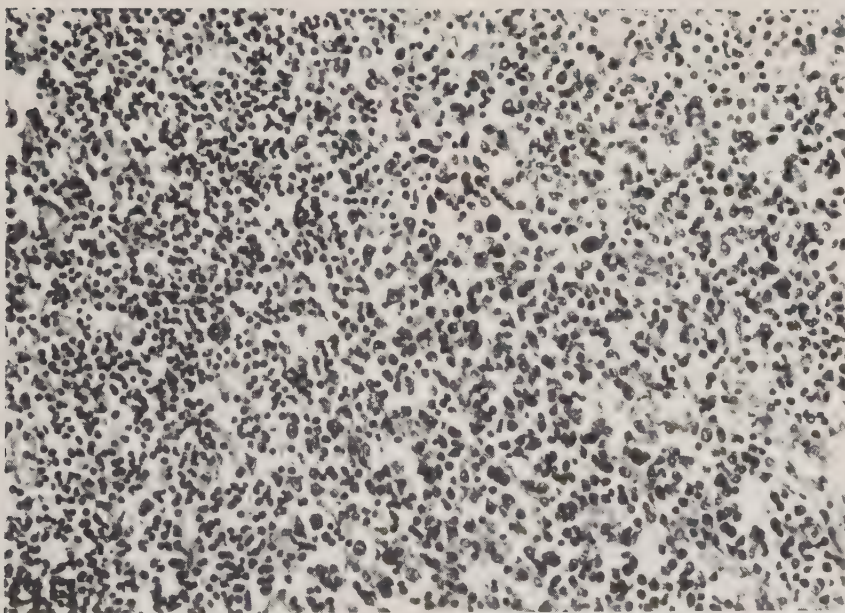
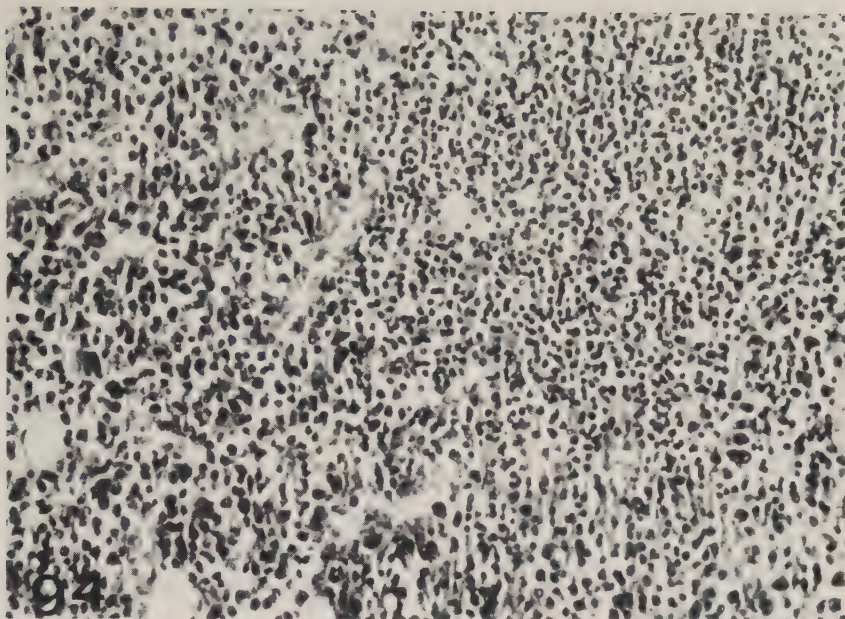


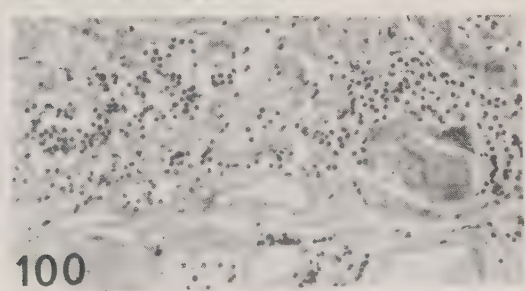
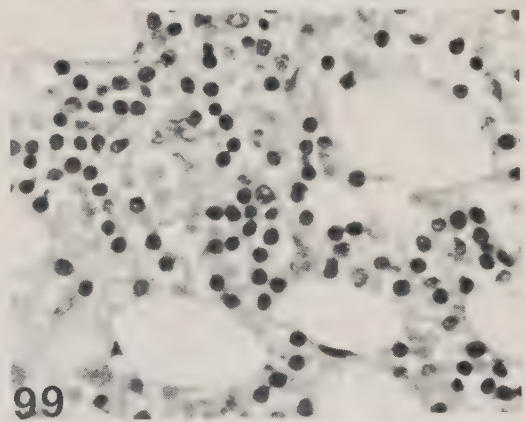
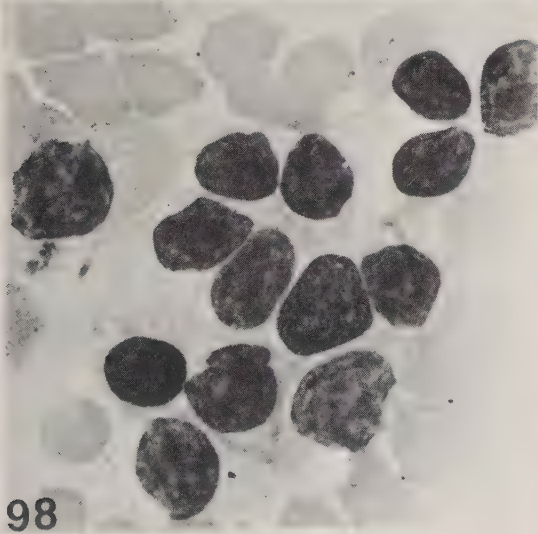
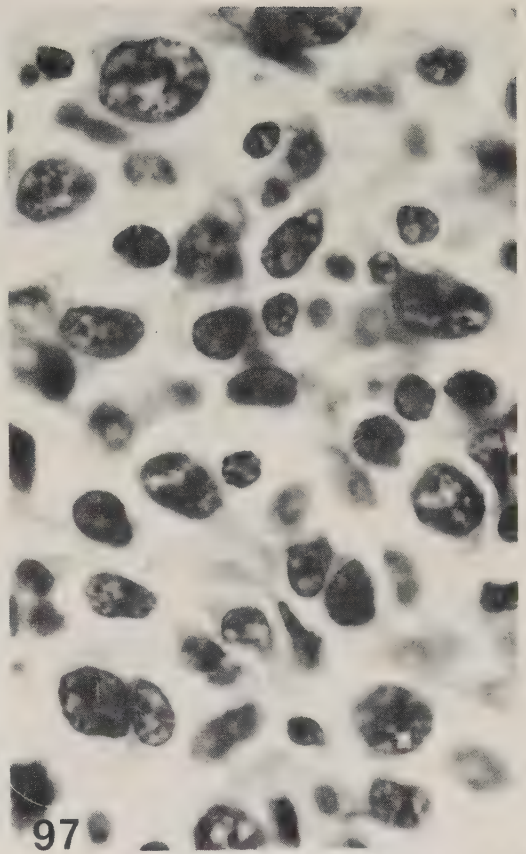
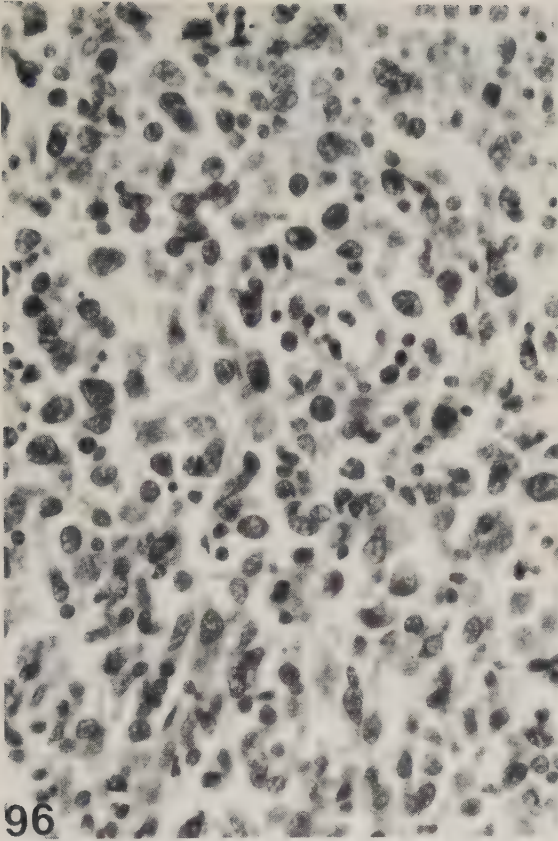
Fig. 96. HL from case 777/68 (Waldenström's macroglobulinemia). Section of inguinal lymph node showing polymorphous infiltrates. x 450.

Fig. 97. Higher magnification of fig. 96. x 1120.

Fig. 98. Bone marrow smear from the time of the diagnosis of case 777/68 (Waldenström's macroglobulinemia), demonstrating classical picture.

Fig. 99. Section of femoral bone marrow obtained at necropsy of case 777/68. Same cytologic picture as that in fig. 98. Compare picture to HL-tumour of figs. 96 and 97. x 450.

Fig. 100. Amyloidosis of cellular infiltrate in case 777/68. Amyloid rings surrounding fat cells and lump of amyloid surrounded by giant cell. Congo red, x 250.



Figs. 101 and 102. Bone marrow smear from case 99/62 (macroglobulinemia). Varying size of tumour cells. Some are very large and plasmacytoid. Most cells contain intranuclear inclusions.

Fig. 103. PAS-staining of bone marrow smear of case 99/62, showing heavy staining of background film and of intranuclear inclusions. No nuclear counter-stain.

Fig. 104. Section of bone marrow obtained at necropsy of case 99/62. Many intranuclear inclusions in most of the abnormal cells. PAS, x 1120.

Fig. 105. Bone marrow smear from case 413/61 (bone marrow group 3). The cells are difficult to classify. Some resemblance to the smear from cases of macroglobulinemia (see for example figs. 83, 84 and 98). However, no obvious plasmacytoid cells.

Fig. 106. LLD-1 + 2. Mediastinal lymph node at necropsy of case 1095/62, demonstrating diffuse mixture of small lymphocytes and immature cells. The picture resembles LLD-2. x 450.

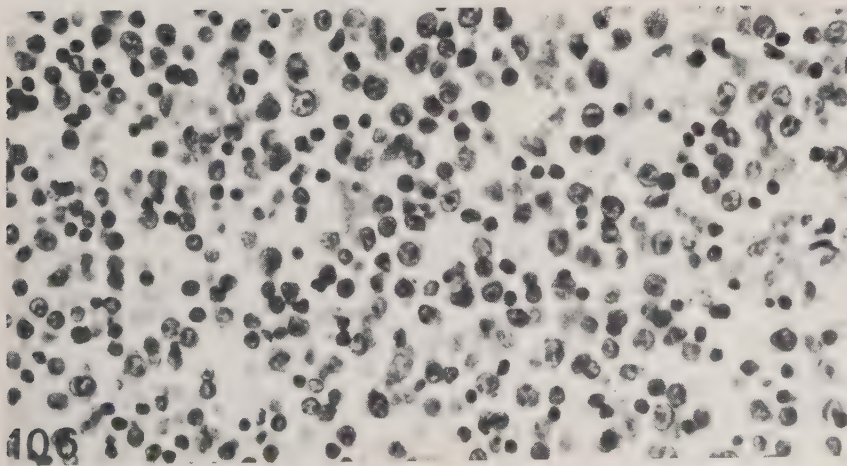
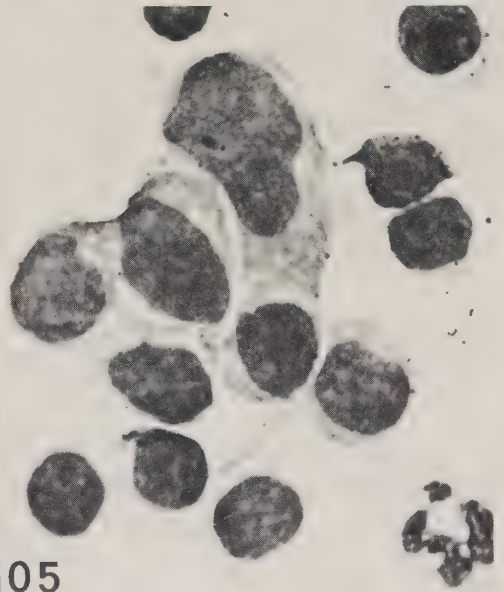
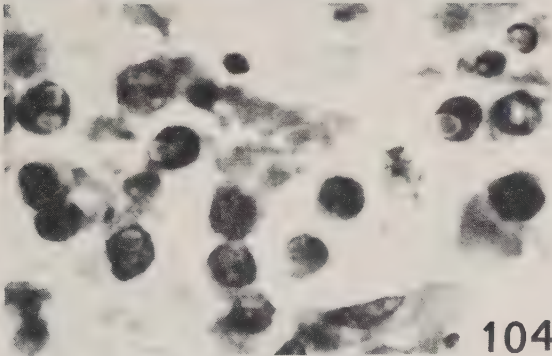
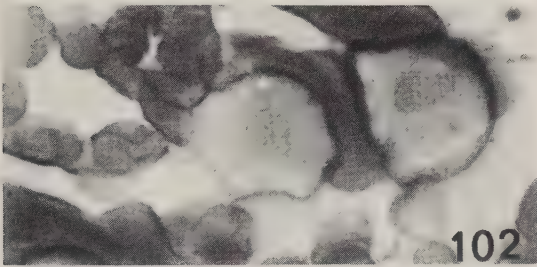
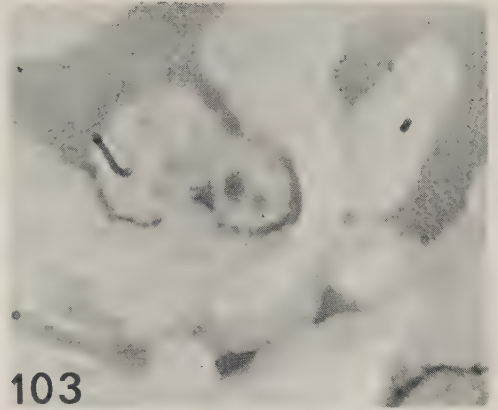
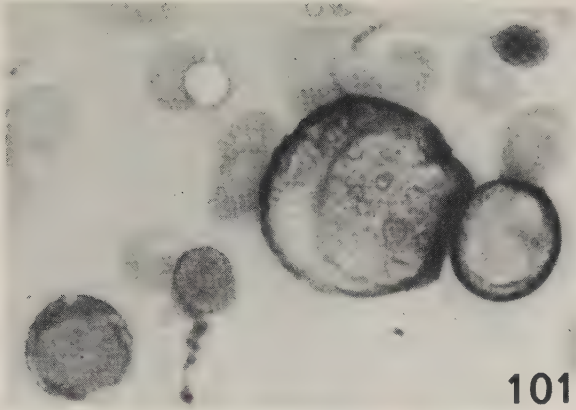


Fig. 107. Tumour of stomach wall of case 737/69 (LLN). In this field many blast cells, but no signs of HL. x 450.

Fig. 108. Splenic tumour in case 737/69, demonstrating nodular HL. Compare fig. 107. x 450.

Fig. 109. Bone marrow smear from case 633/68. Necropsy specimens of lymph nodes obtained shortly after this bone marrow smear showed picture of undifferentiated malignant lymphoma. Many blast cells in this field, but also many atypical lymphocytic cells.

Fig. 110. Bone marrow smear of case 878/64. The picture resembles blastic leukemia. This patient had already 50 months earlier the picture of undifferentiated malignant lymphoma in a mediastinal tumour. By that time appearance of the bone marrow was normal.

Fig. 111. Blood picture in terminal phase of case 878/64, demonstrating cells of lymphocytic size, but atypical and sometimes with immature nuclear structure. Compare fig. 110.

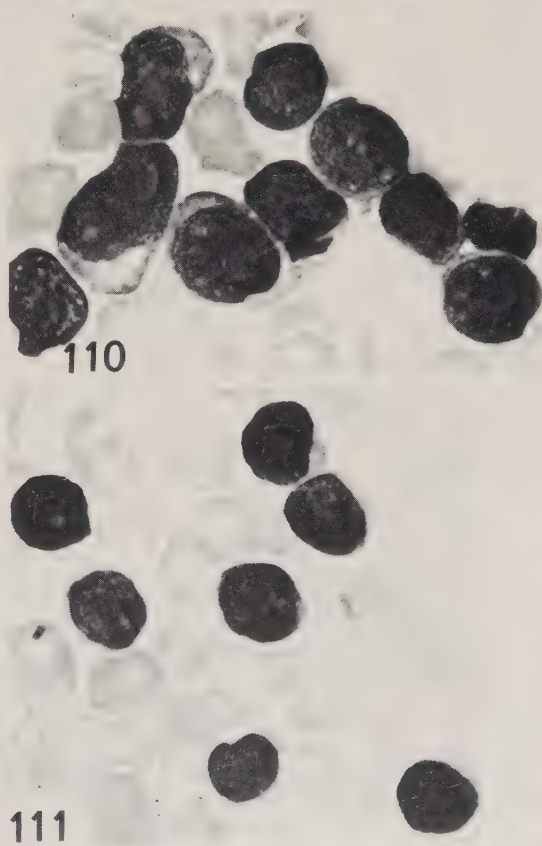
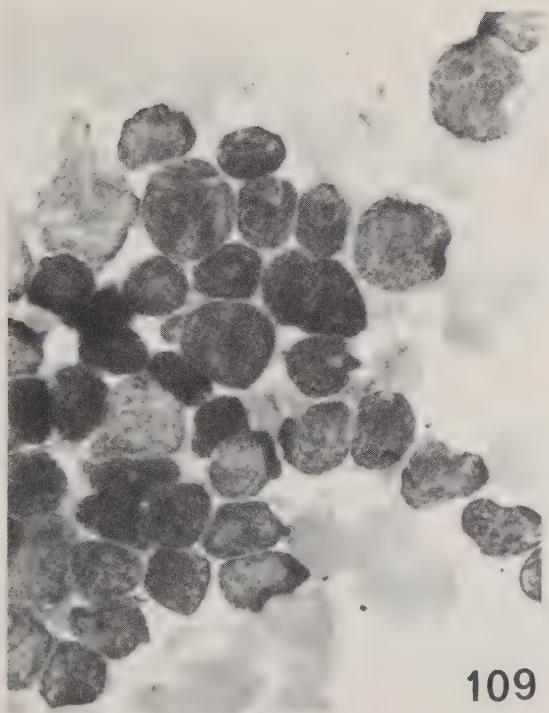
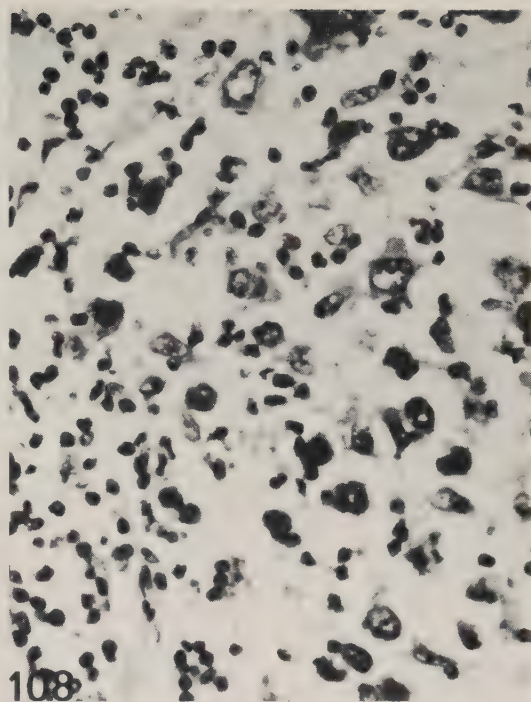
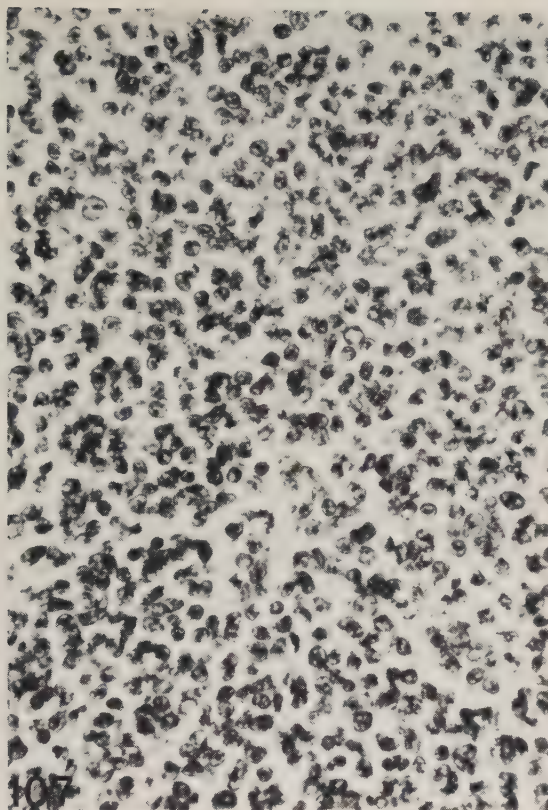


Fig. 112. LLD-1. Lymph node obtained at necropsy of case 98/58, showing IF-n. At this magnification the foci are identical to the IF of biopsy specimens, but they are often better demarcated. x 25.

Fig. 113. Higher magnification of node in fig. 112, showing 2 prominent IF-n separated by a field of mature lymphocytes. x 170.

Fig. 114. High magnification of IF-n. Cells are similar to those of IF in biopsy specimens (compare with fig. 2). There are, however, many atypical cells with irregular and hyperchromatic nuclei and recognition of the different "generations" is not so easy as in the more orderly picture of the IF of biopsy specimens. Atypical mitotic figure at arrow. x 670.

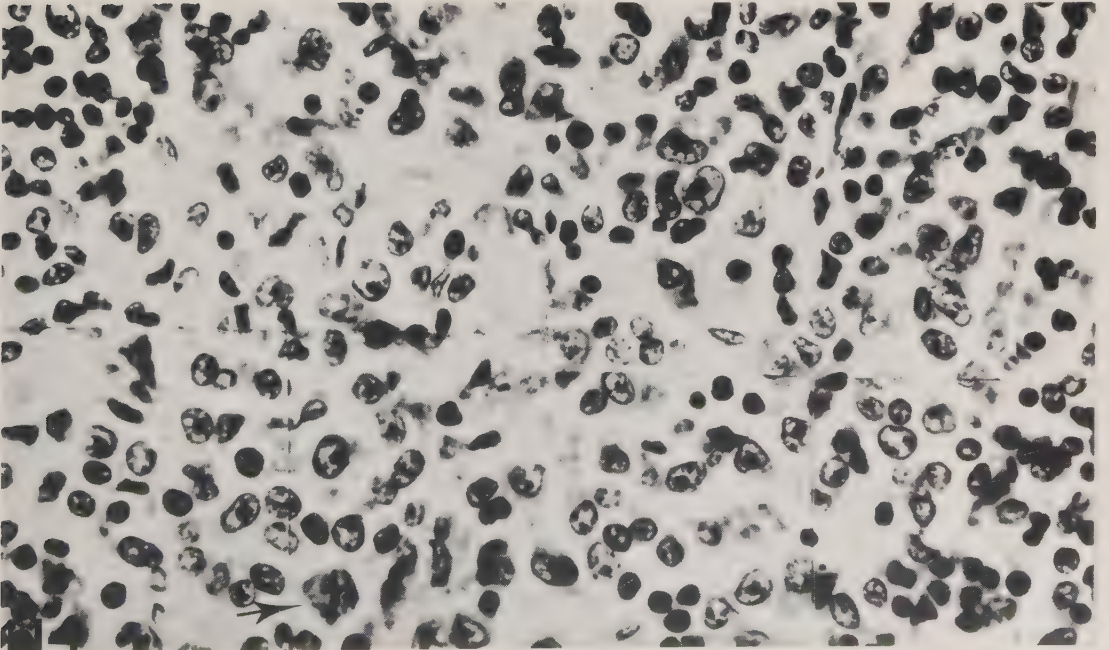
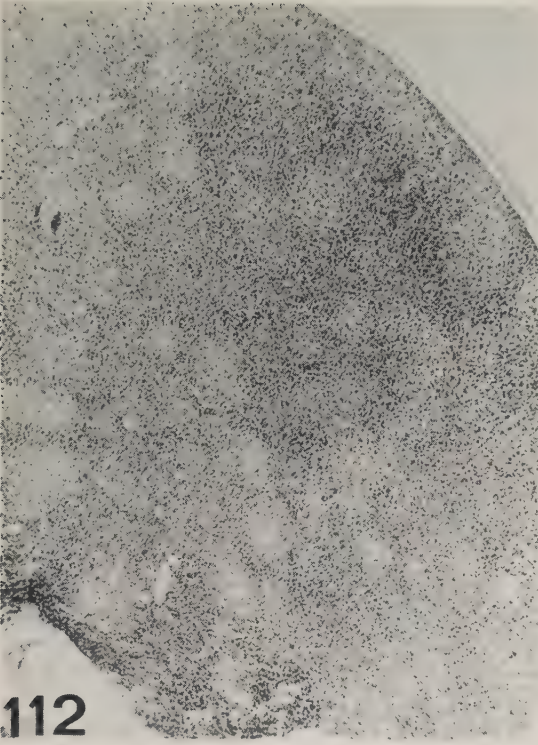


Fig. 115. Hepatic focus of Hodgkin's disease in case 31/67 (LLD-1). Necrosis in the centre, in the periphery a brim of lymphocytic infiltration, in between a polymorphous granulation tissue. x 90.

Fig. 116. Higher magnification of fig. 115. Picture is characteristic of Hodgkin's disease with many multinucleated Reed-Sternberg cells and fibrosis. x 450.

Fig. 117. Another part of the field in fig. 115. Many macrophages with phagocytosis of lymphocytes. x 1120.

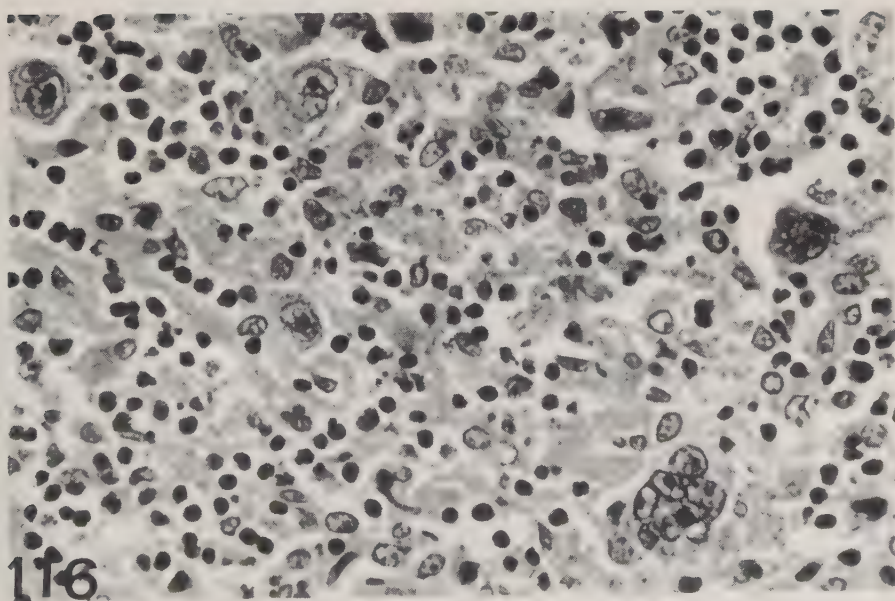
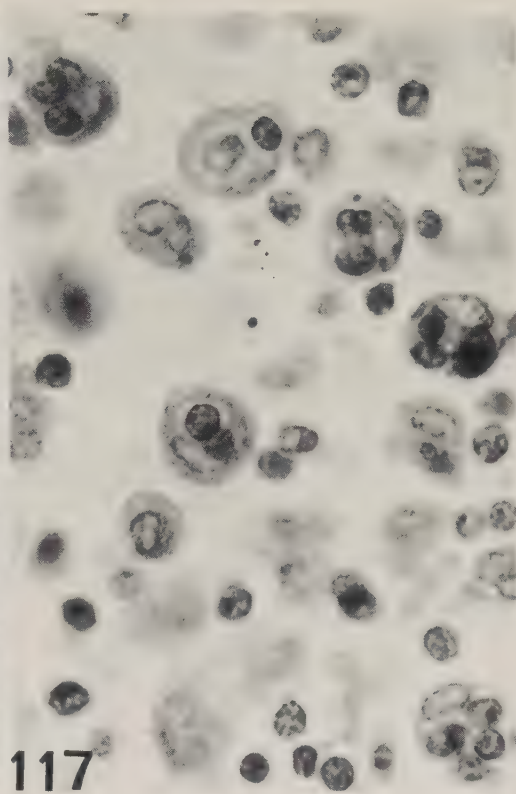
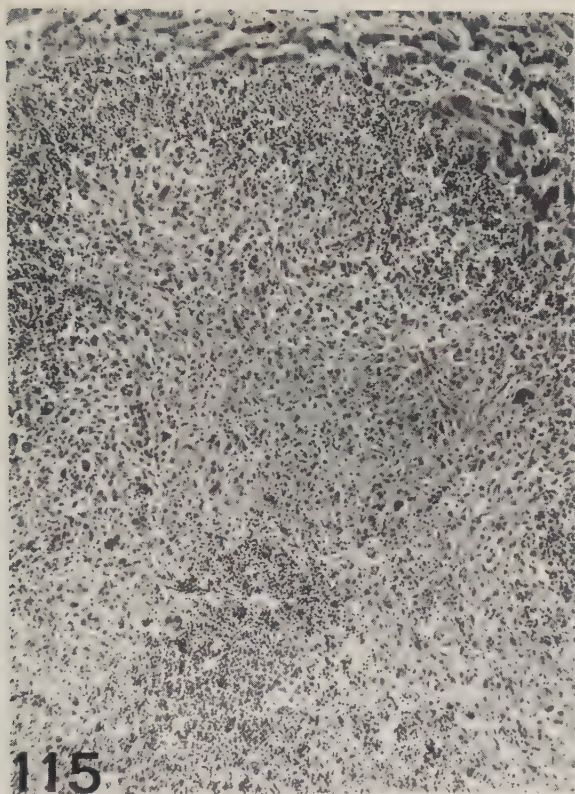


Fig. 118. Splenic focus of Hodgkin's disease in case 692/66 (LLD-1). Reed-Sternberg cells and macrophages and many prolymphocytes. x 450.

Fig. 119. Hepatic foci of Hodgkin's disease in case 692/66. Many large tumour nodules, partly confluent, with destruction of liver parenchyma. x 30.

Fig. 120. Reed-Sternberg cell in smear of lymph node aspirate from a patient with CLL of 4 years standing. The patient was taken ill with a febrile disease after having been in good clinical condition for several years. The nodes grew rapidly. The patient died within a short time. Case not part of this study. x 1300.

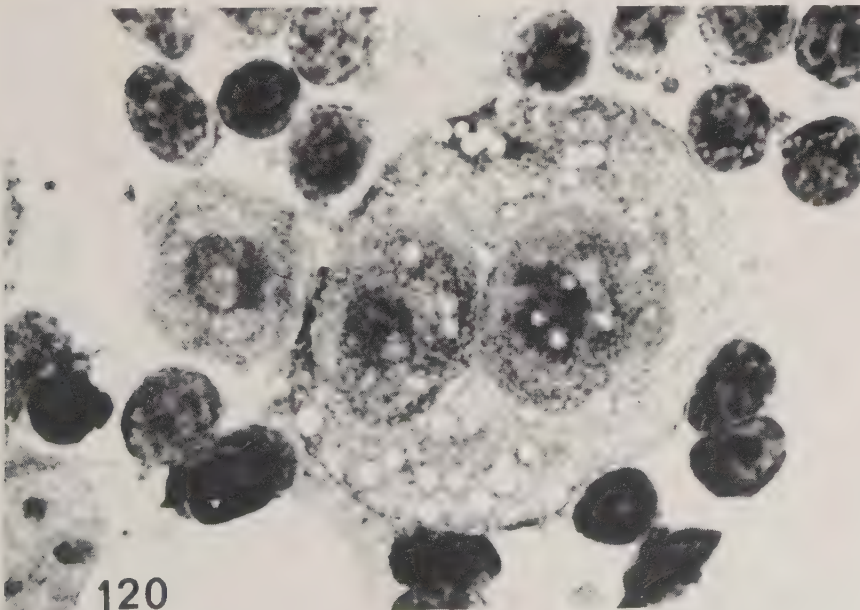
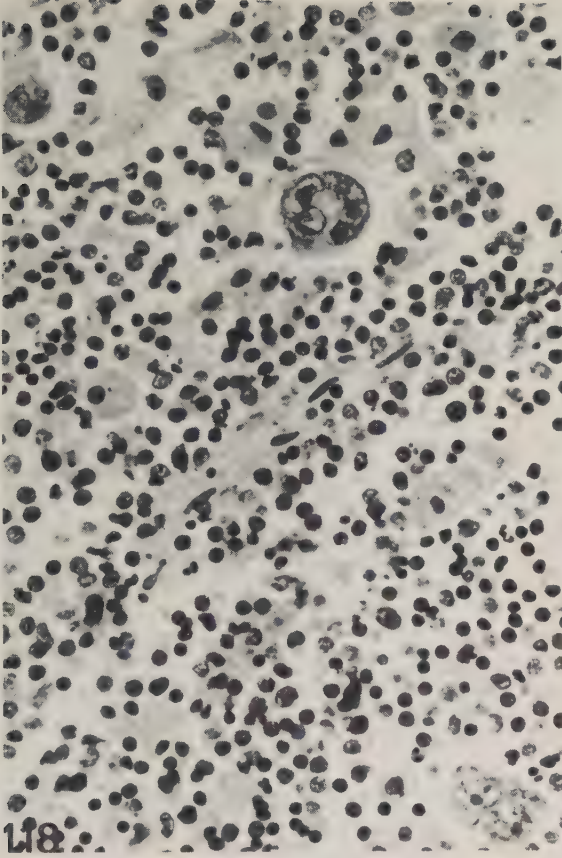
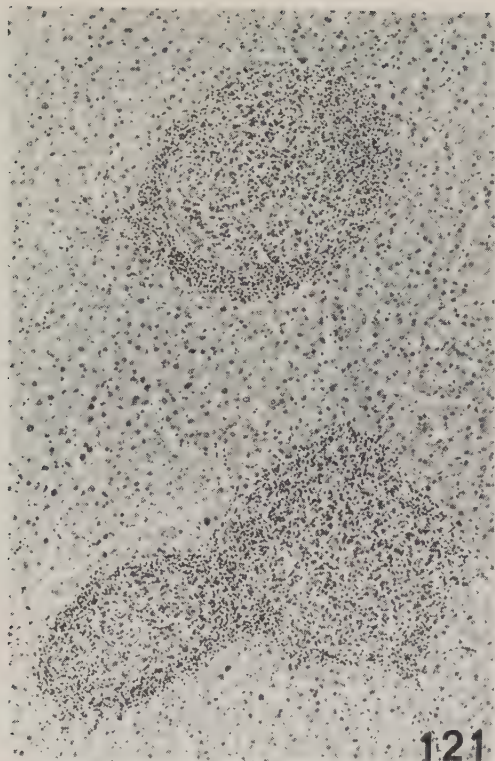


Fig. 121. Case 1298/65 (LLD-1). Coalescent periportal lymphocytic infiltrates with central foci of HL. x 70.

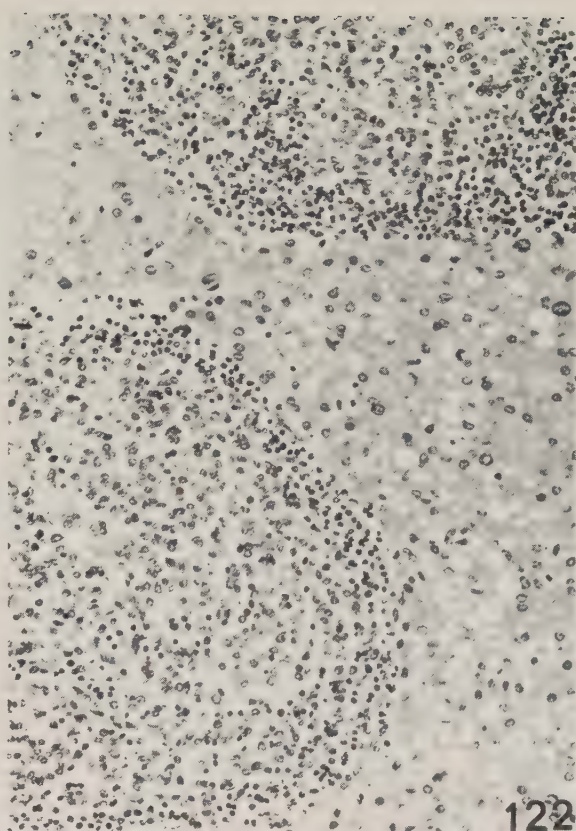
Fig. 122. Higher magnification of fig. 121. Note lymphocytic brim around HL-tissue. x 180.

Fig. 123. Higher magnification of fig. 122. Note rather abrupt transition between lymphocytic and histiocytic parts. x 450.

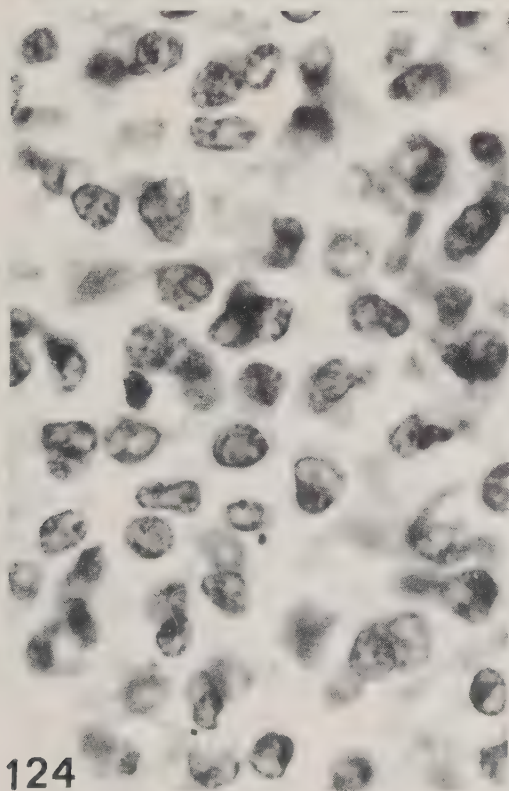
Fig. 124. Higher magnification of HL-tissue in fig. 123. x 1120.



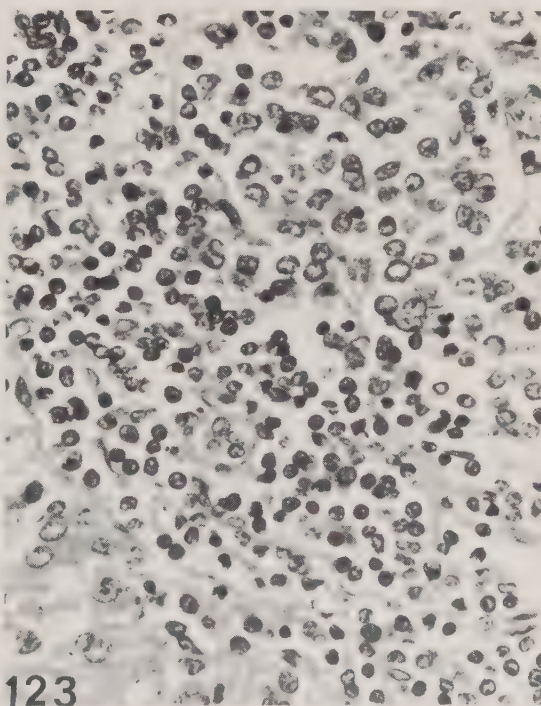
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Fig. 125. Case 1298/65 (LLD-1). Coalescent IF-n with transition to HL (lower part) in a lymph node. x 20.

Fig. 126. HL in stomach wall of case 83/64 (LLD-1). Mucosal surface at top. x 20.

Fig. 127. HL of case 831/70 (LLD-1). Polymorphous tumour tissue infiltrating muscle of thoracic wall. x 420.

Fig. 128. Higher magnification of fig. 127. Note mixture of lymphocytes and HL-cells. x 1120.

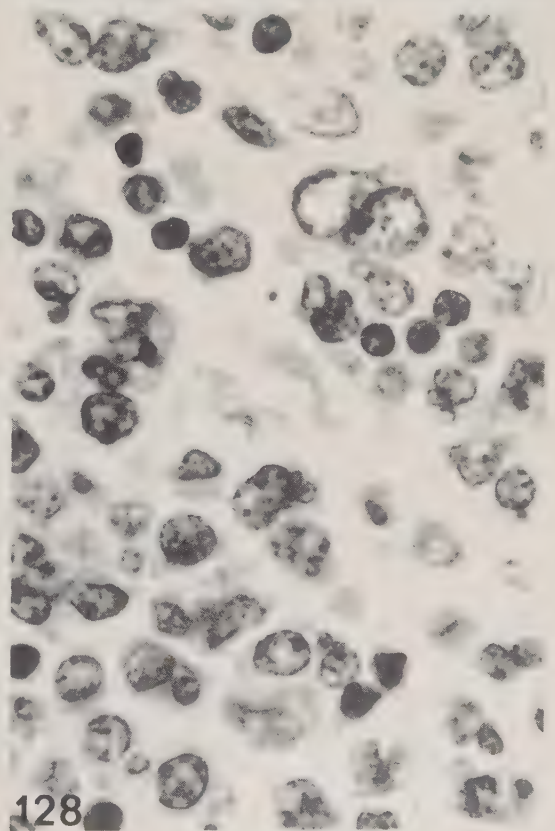
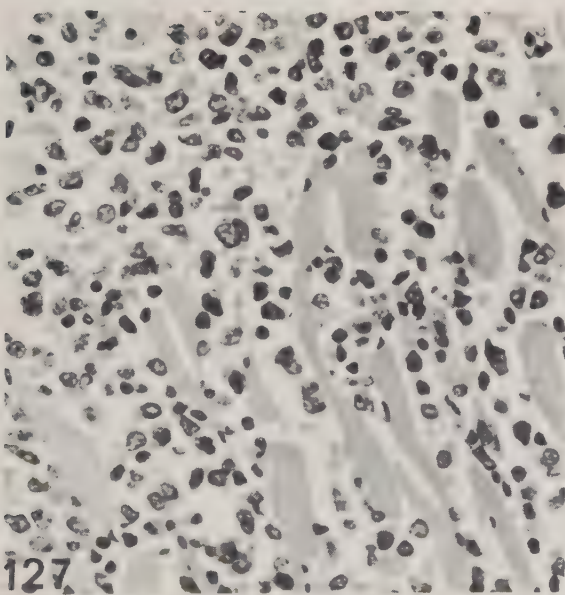
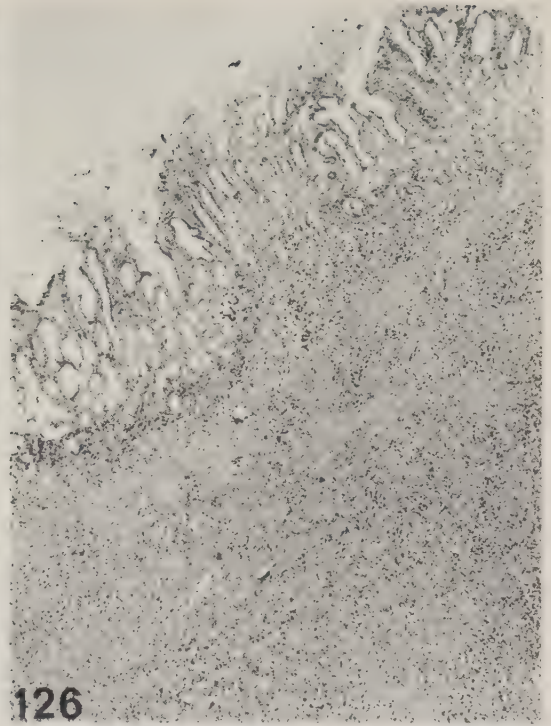
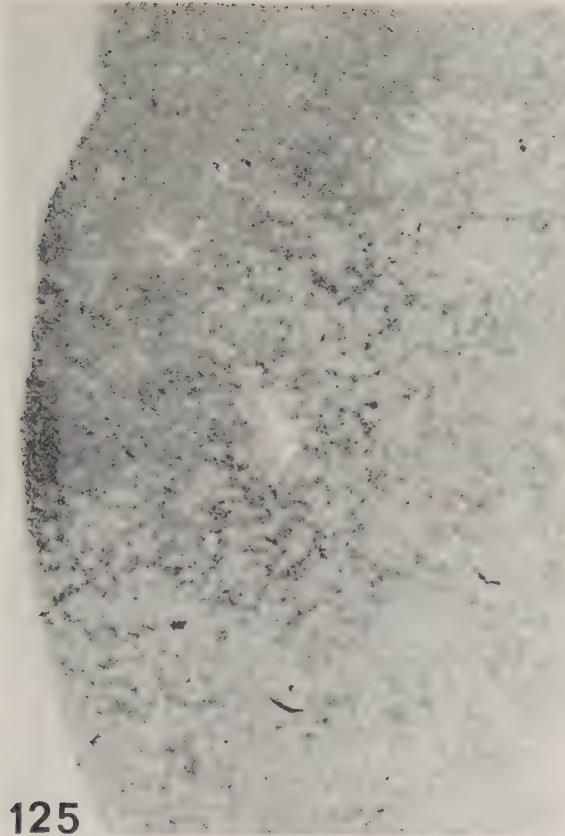


Fig. 129. Lymph node of case 42/65 (LLD-1). Marginal sinus filled with polymorphous, histiocyte-like cells. Similar cells spread along the sinus within the parenchyma. Toluidine blue, x 180.

Fig. 130. Focus of HL within the parenchyma of the node in fig. 129. Toluidine blue, x 1120.

Fig. 131. High power view of cells within sinus of the node in fig. 129. Note seeming association of cells with reticulum fibres. Toluidine blue, x 1120.

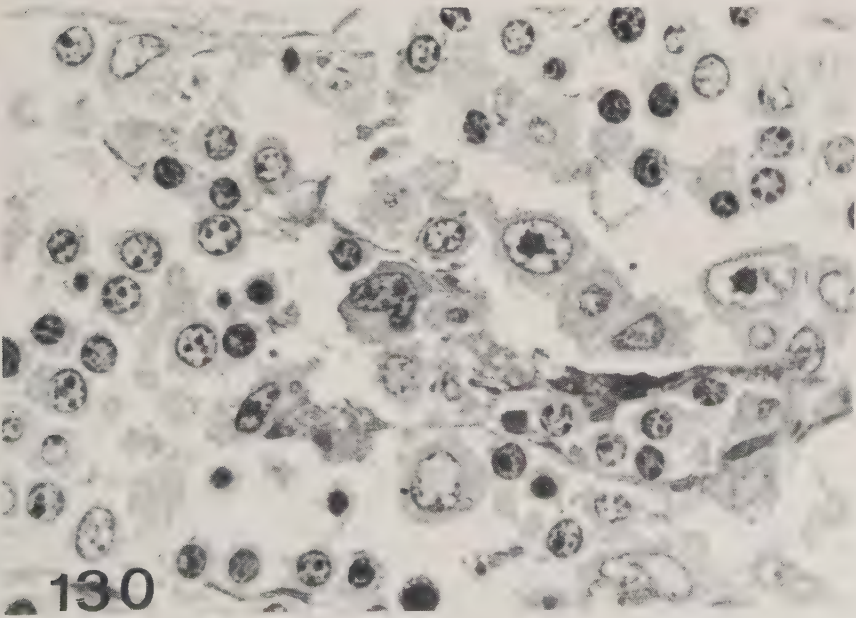
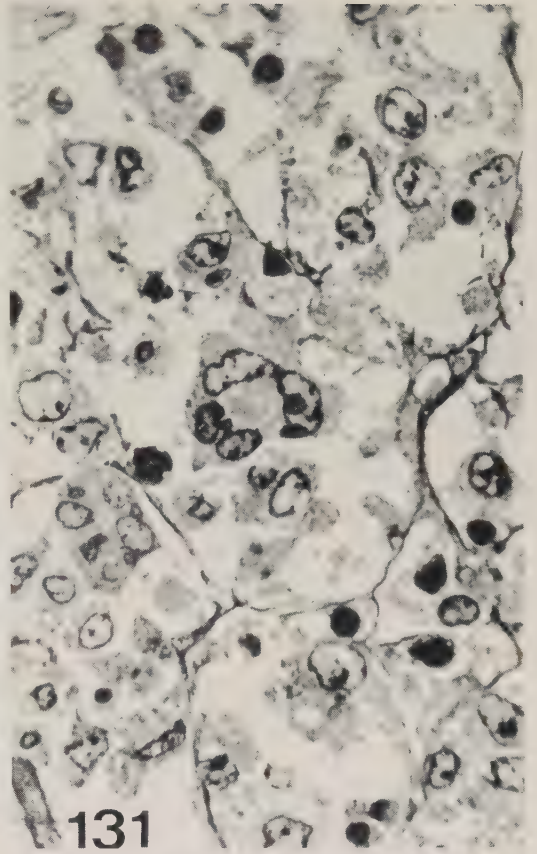
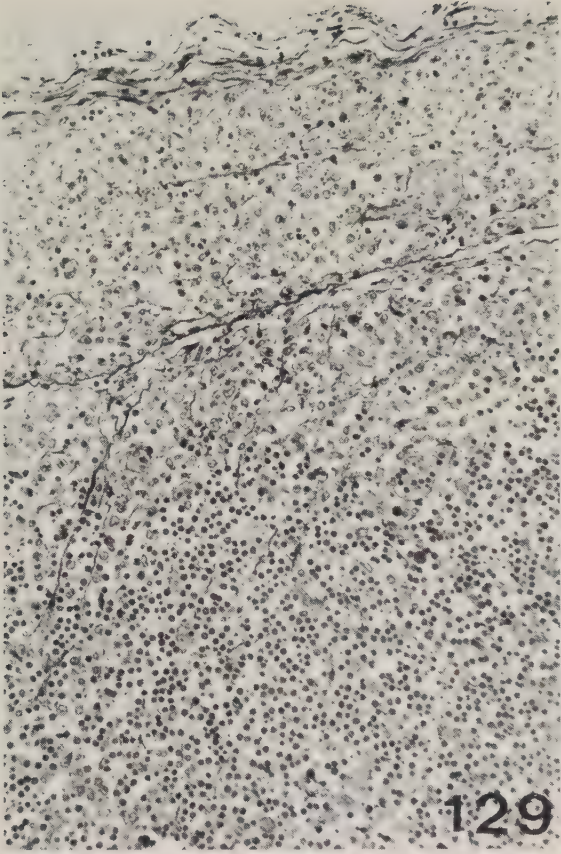


Fig. 132. Hepatic nodule of HL in case 42/65 (LLD-1). Very polymorphous tumour tissue mixed with lymphocytes. x 180.

Fig. 133. Lung infiltrate of case 42/65 (LLD-1). Lymphocytic infiltration of interstitial tissue with atypical cells, also seen within the alveoli. x 150.

Fig. 134. HL in lymph node of case 1434/64 (LLD-1). Predominantly immunoblastic type. Two mitotic figures in the field. x 1120.

Fig. 135. HL in lymph node of case 136/58 (LLD-1). The cells are very "histiocytic" in appearance. Mitotic figure below centre. x 450.

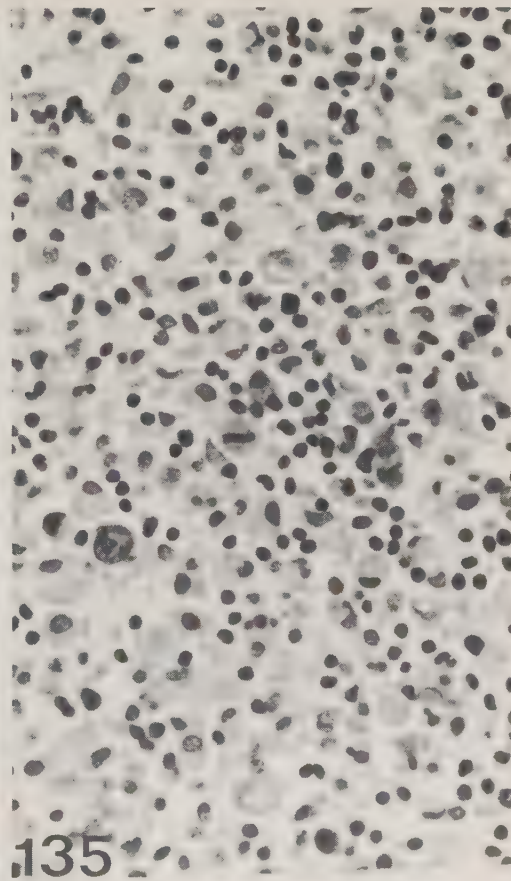
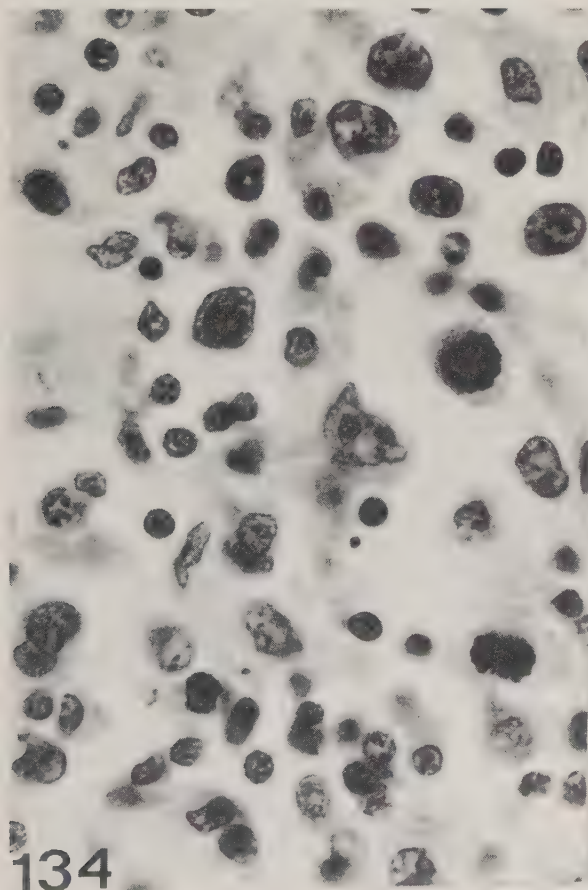
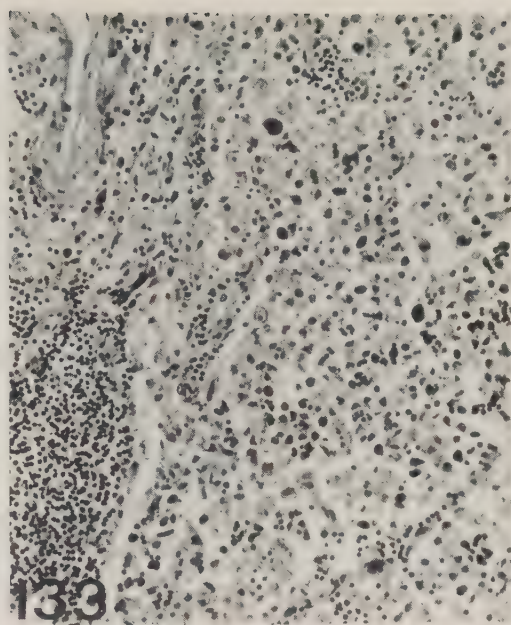
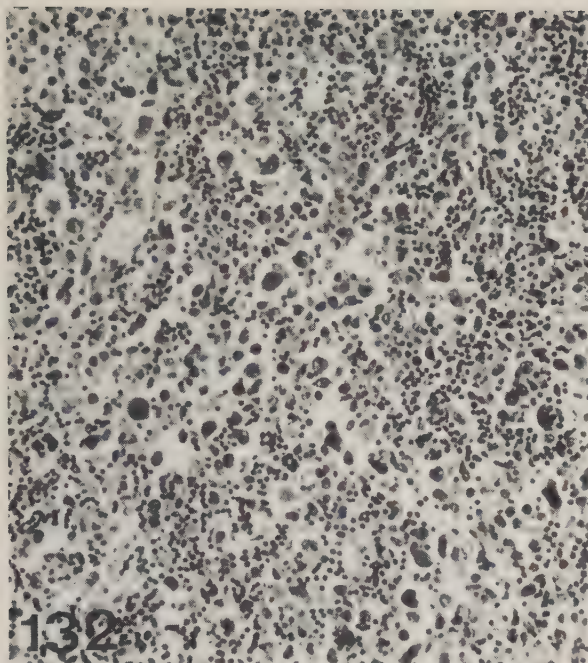


Fig. 136. Case 961/61 (LLD-1). Necropsy specimen of femoral bone marrow, showing lymphocytic infiltration. x 450.

Fig. 137. Appearance of bone marrow smear at the time of the diagnosis of case 961/61. Cytological picture in fig. 136 unchanged.

Fig. 138. Lymph node from case 961/61. Transitional zone between lymphocytic infiltration and HL, demonstrating many connective tissue fibres. van Gieson, x 160.

Fig. 139. HL in lymph node of case 961/61. Fascicular growth. van Gieson, x 70.

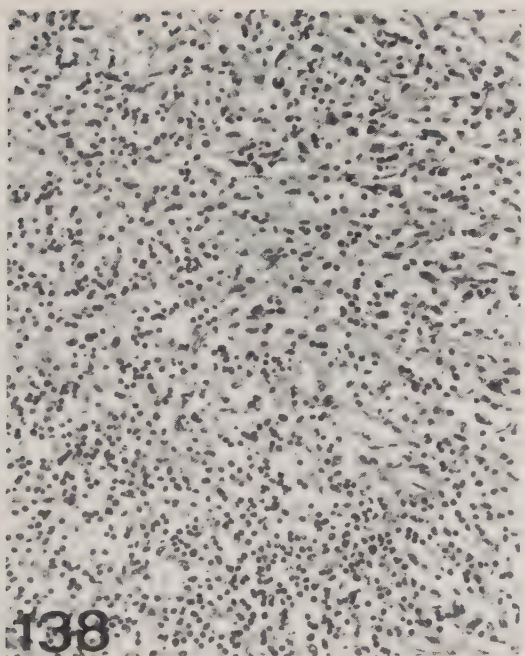
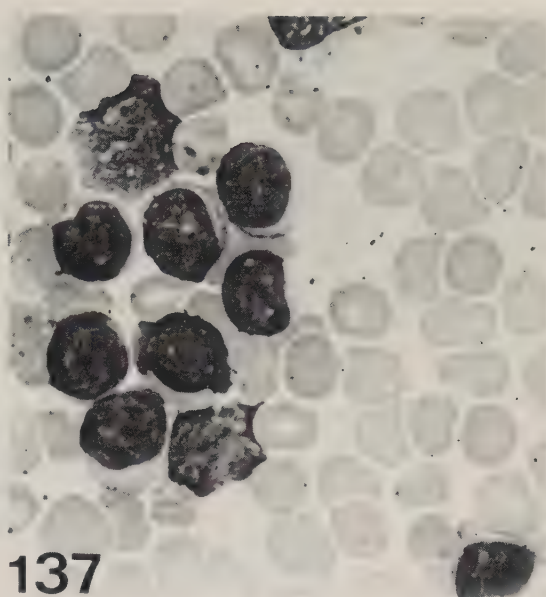
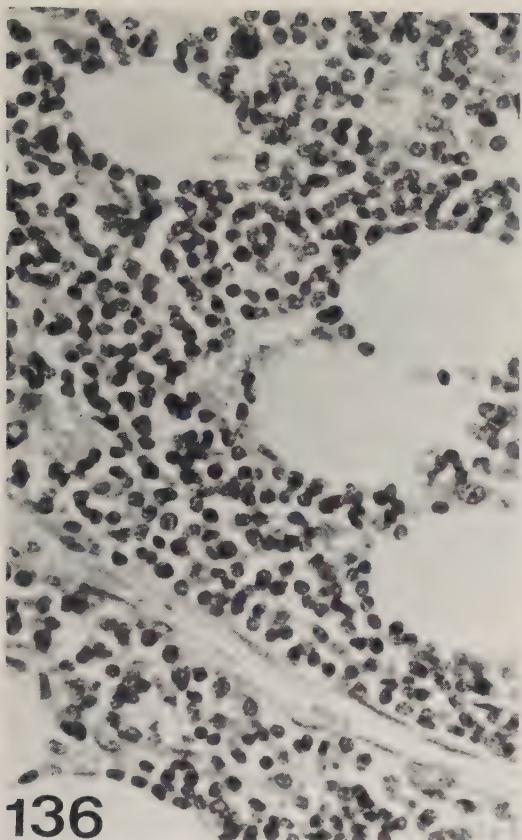


Fig. 140. Higher magnification of fig. 139. x 180.

Fig. 141. Higher magnification of fig. 140. x 450.

Fig. 142. Higher magnification of fig. 141. Spindle-shaped tumour cells and many plasmacytoid forms. Compare cytological picture to that of bone marrow, figs. 136 and 137. x 1120.

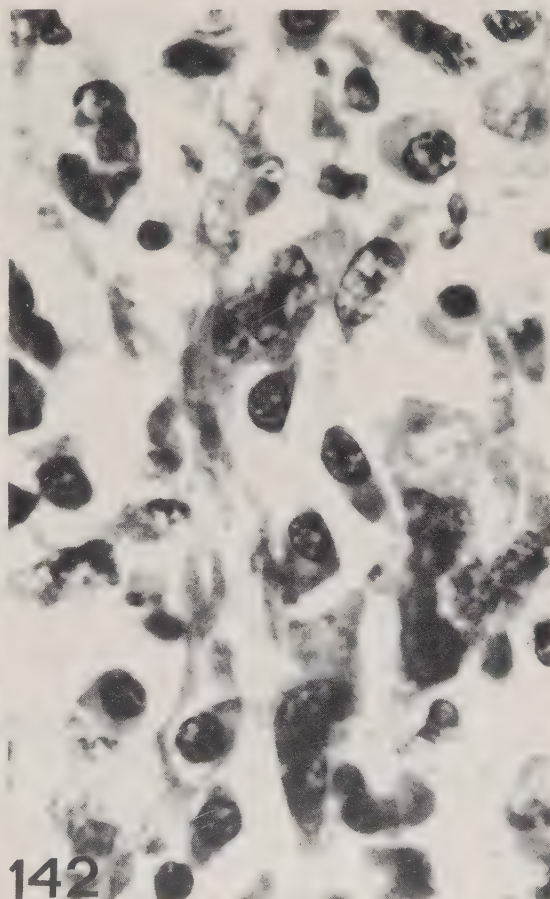
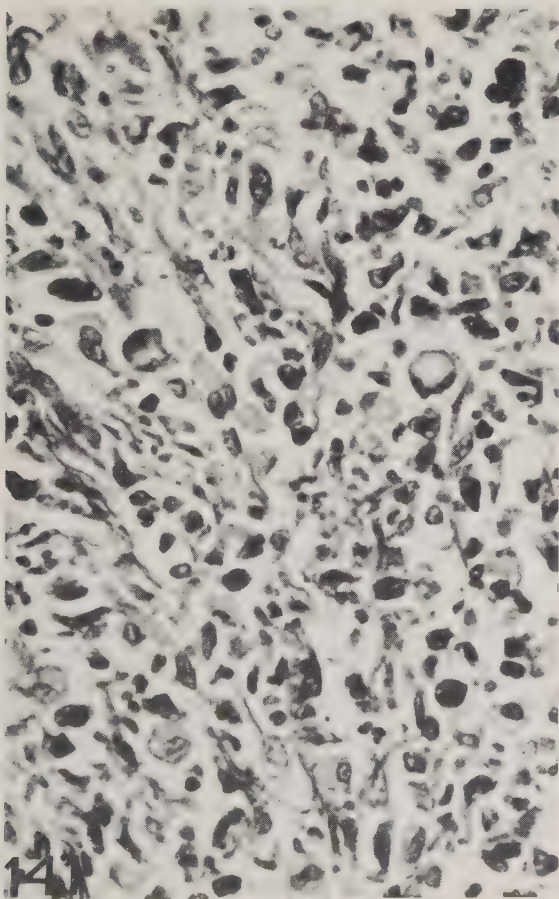
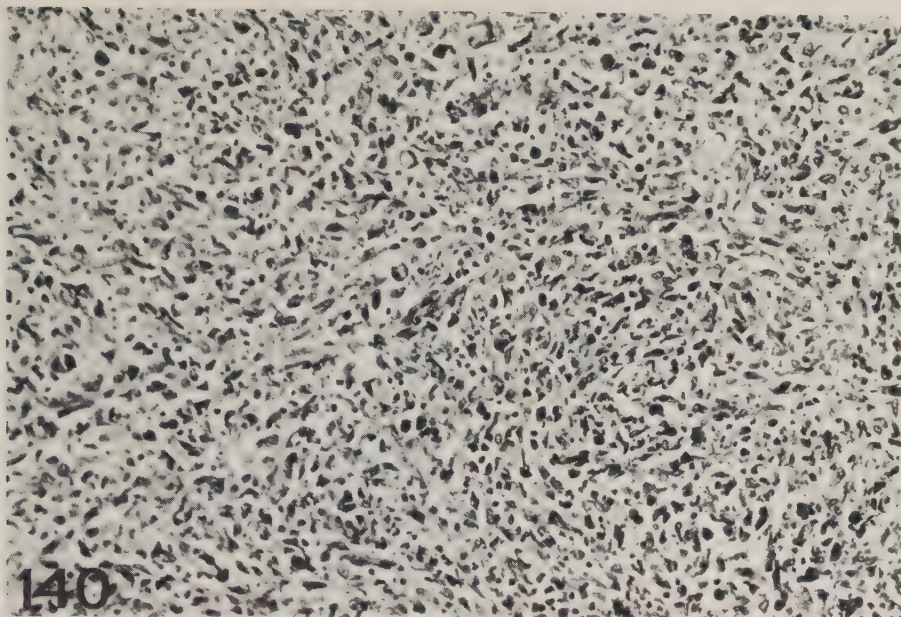
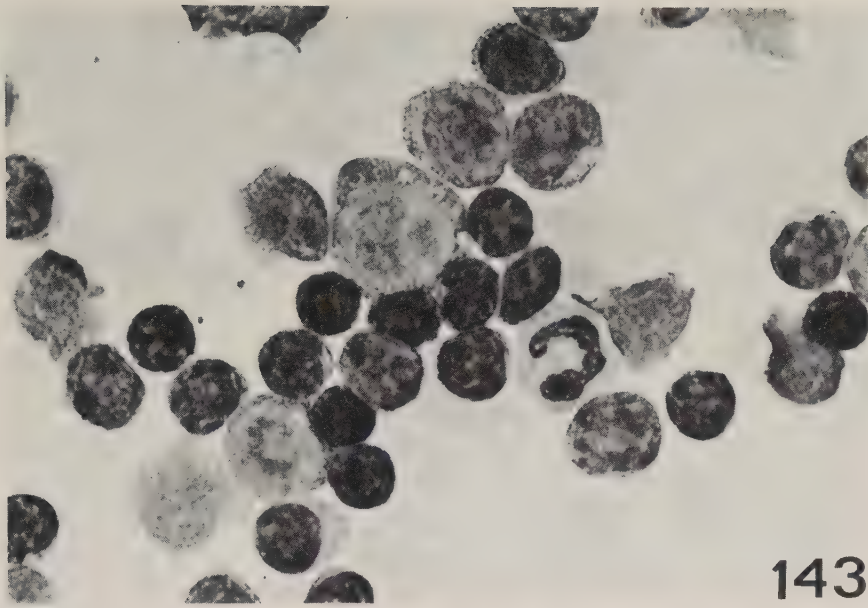


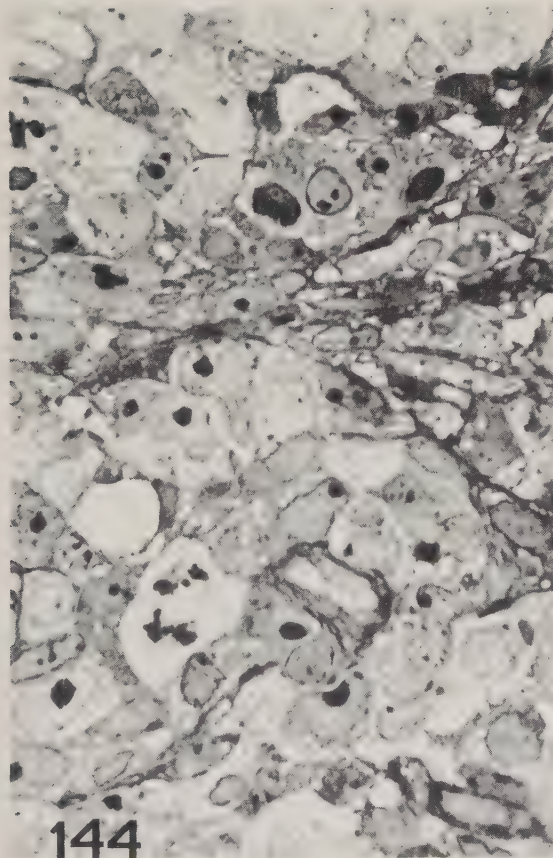
Fig. 143. Bone marrow smear from late phase of case 669/73 (LLD-1). Many lymphocytes, some prolymphocytes, and one large, immature cell, possibly IF-2 cell.

Fig. 144. Gingival HL-tumour of case 669/73 (LLD-1). Mainly immunoblastic type with prominent nucleoli. Mitotic figure in lower part of picture. Toluidine blue, x 1120.

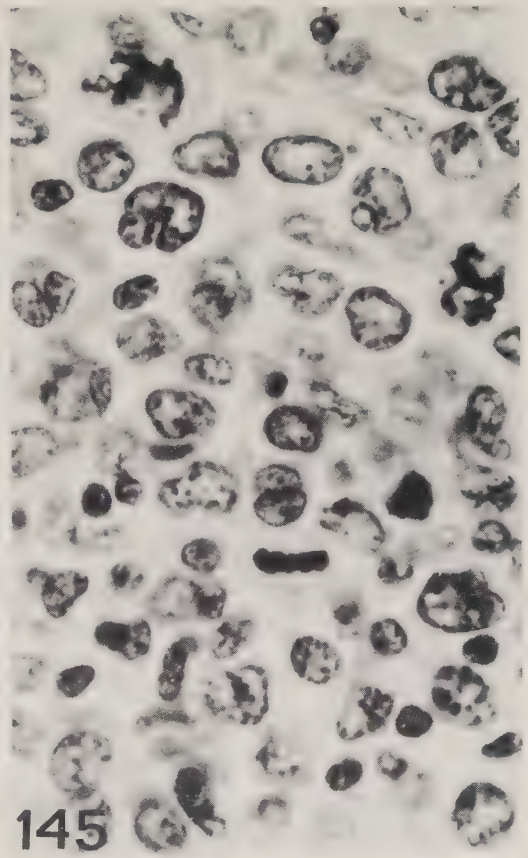
Fig. 145. Appearance of HL-tissue in necropsy specimen from the liver of case 669/73. Nucleoli less prominent in autolysed tissue. Cells appear more polymorphous than in fig. 144. Many mitotic figures. x 1120.



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Fig. 146. Lymph node biopsy of case 829/69 (LLD-1). Transition from lymphocytic tissue (upper left) to confluent IF, forming brim around HL-focus (not seen in this picture). x 450.

Fig. 147. High power view of zone with coalescent IF in lymph node biopsy specimen from case 829/69. Occasional cells difficult to assign to any of the IF-cell categories described in the text. Such cells as are seen at arrows have atypia, which may correspond to that seen in IF of necropsy specimens. Toluidine blue, x 1120.

Fig. 148. Very small collection of immature cells in lymph node biopsy specimen from case 829/69. This appearance probably represents the initial phase of an IF. The two large cells in the upper part of the picture probably represent telophase of an IF-1 mitosis. In lower left part of the picture some IF-2 cells. Arrows point to some prolymphocytes. Small venule in upper part of the picture. Toluidine blue, x 1120.

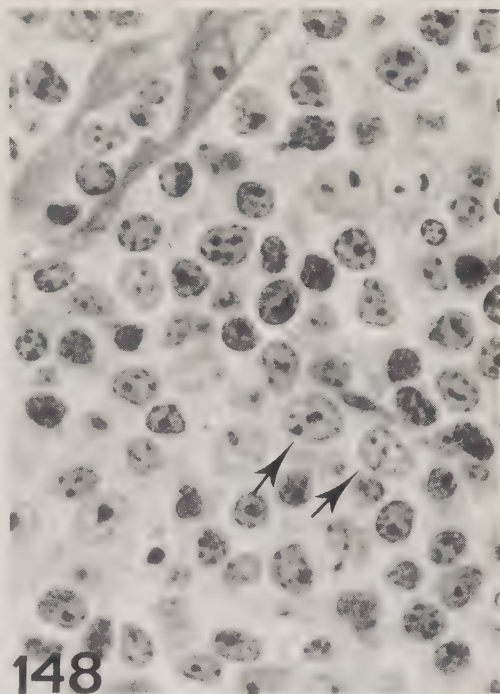
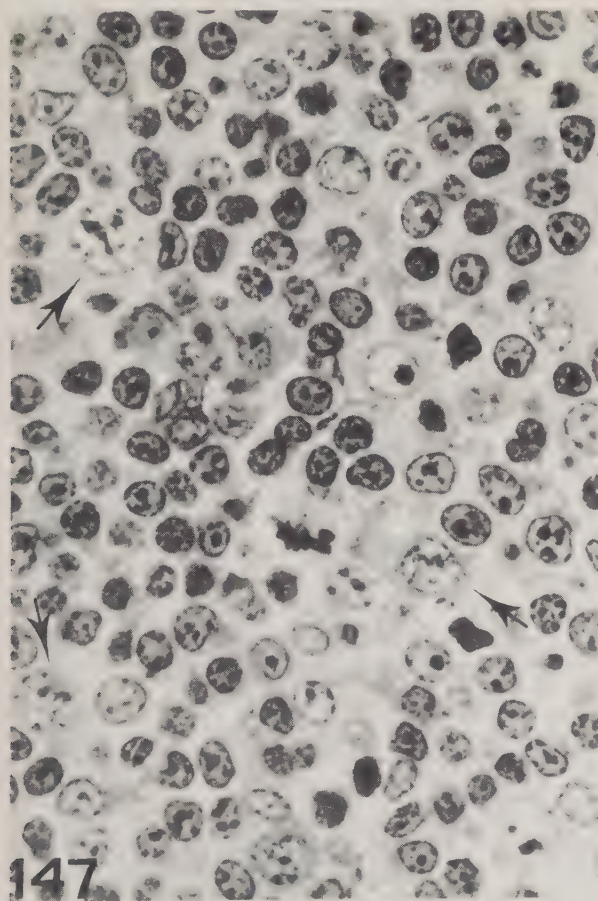
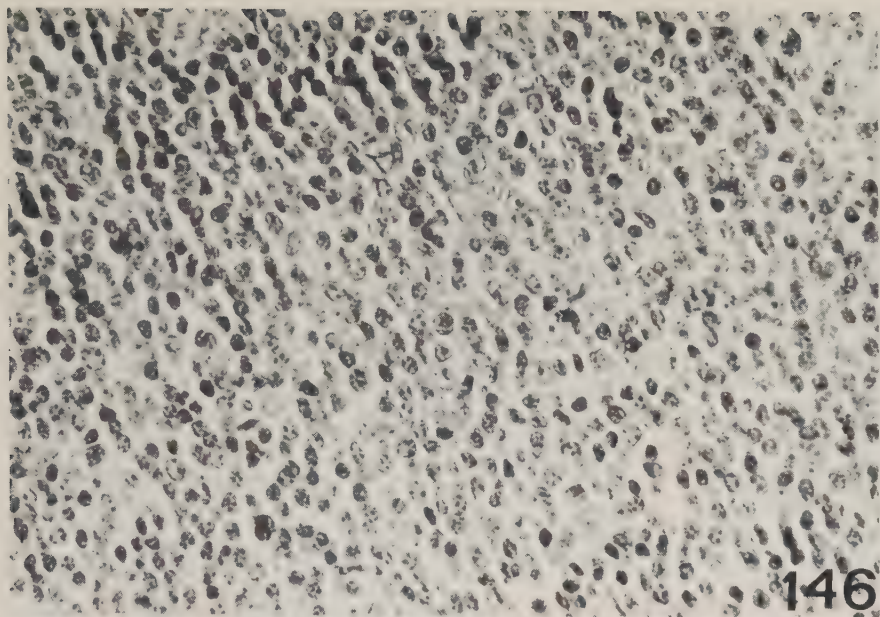


Fig. 149. Lymph node aspirate of a node not affected by HL in case 829/69 (LLD-1). Compare with fig. 153.

Fig. 150. Electron micrograph of the node illustrated in fig. 149. Some pro-lymphocytes are seen and part of 2 IF-2 cells (left and top right). Note many peculiar densities at contact points (arrows). Some seem to be situated within the cytoplasm depending on invaginations of cell surface. x 8000.

Fig. 151. Higher magnification of structure seen in fig. 150. The cells have interwoven processes with collection of dense material in cytoplasm. Inter-cellular space bridged by paired spicules within this zone. x 60,000.

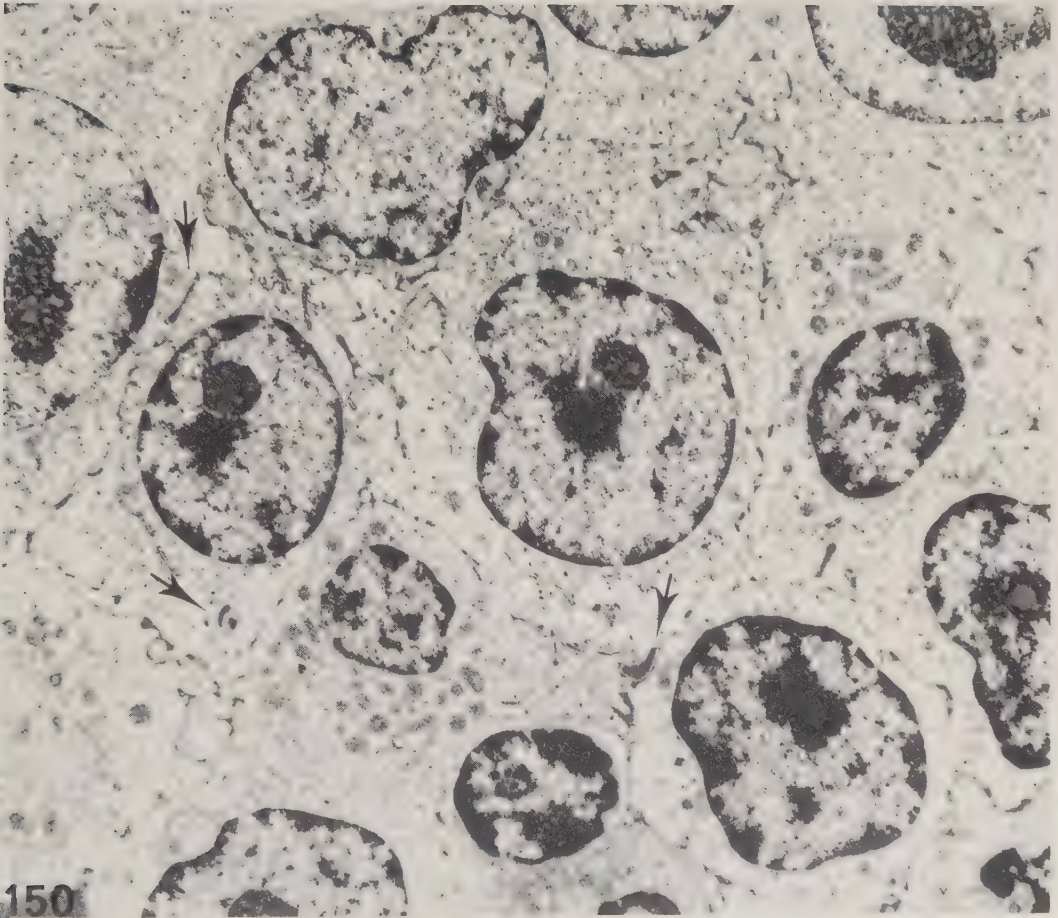
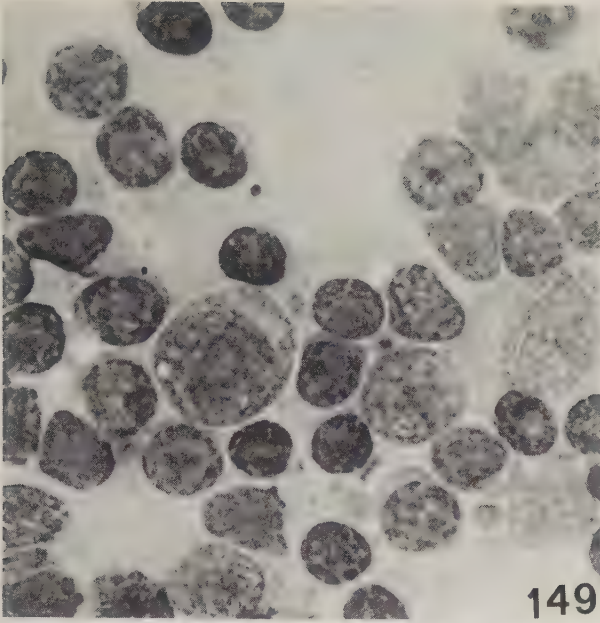


Fig. 152. Lymph node biopsy specimen from case 829/69. Transition between zone of coalescent IF (lower right) and HL. Light spaces between HL-cells represent macrophages. x 180.

Fig. 153. Fine-needle aspirate from node illustrated in fig. 152. Large, immature cell, probably HL-cell. The majority of cells are lymphocytes and prolymphocytes. Compare fig. 149.

Fig. 154. High power view of HL-tissue illustrated in fig. 152. Many cells have markedly plasmacytoid features (arrows). Toluidine blue, x 1120.

Fig. 155. HL-tissue in lymph node biopsy in case 829/69. Dead tumour cells are phagocytised within macrophages. Seeming dense intranuclear inclusion body in one of the cells. Such inclusion bodies were often seen and electron microscopically they consisted of granular or structureless detritus. Virus-like particles were never seen in them. Toluidine blue, x 1120.

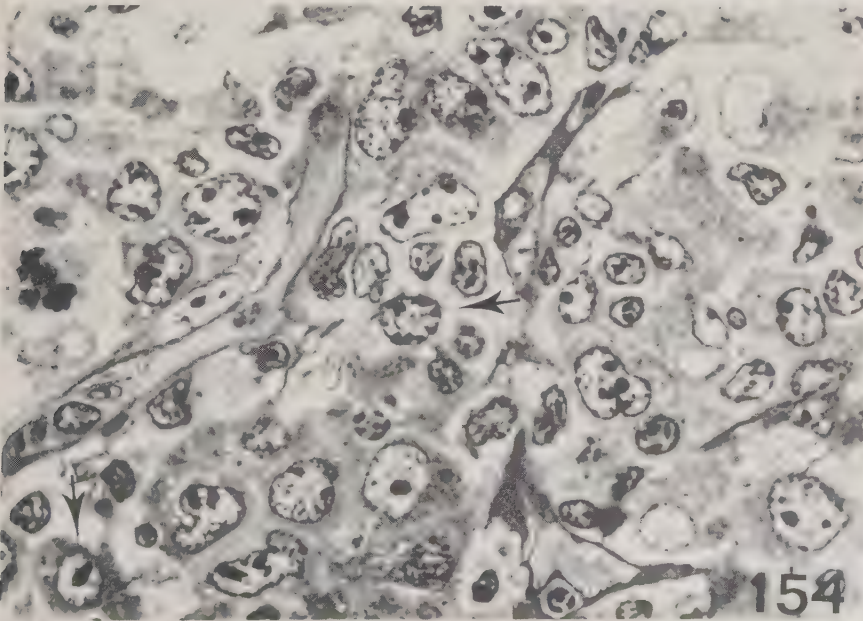
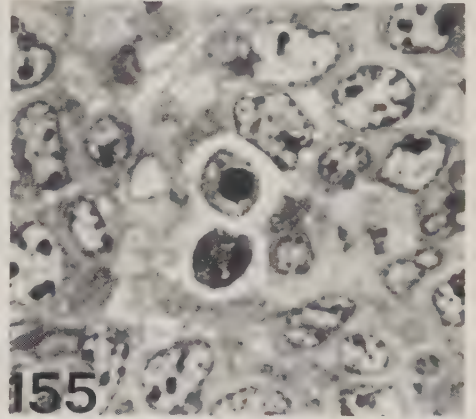
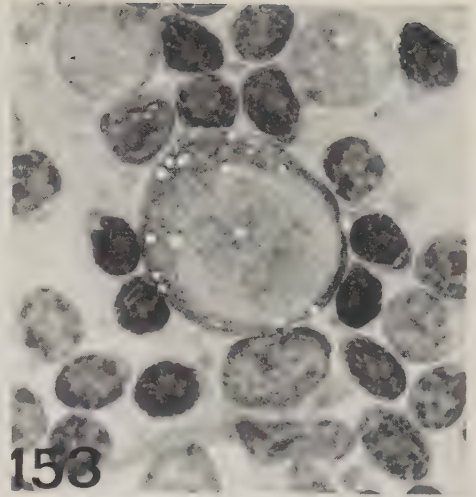
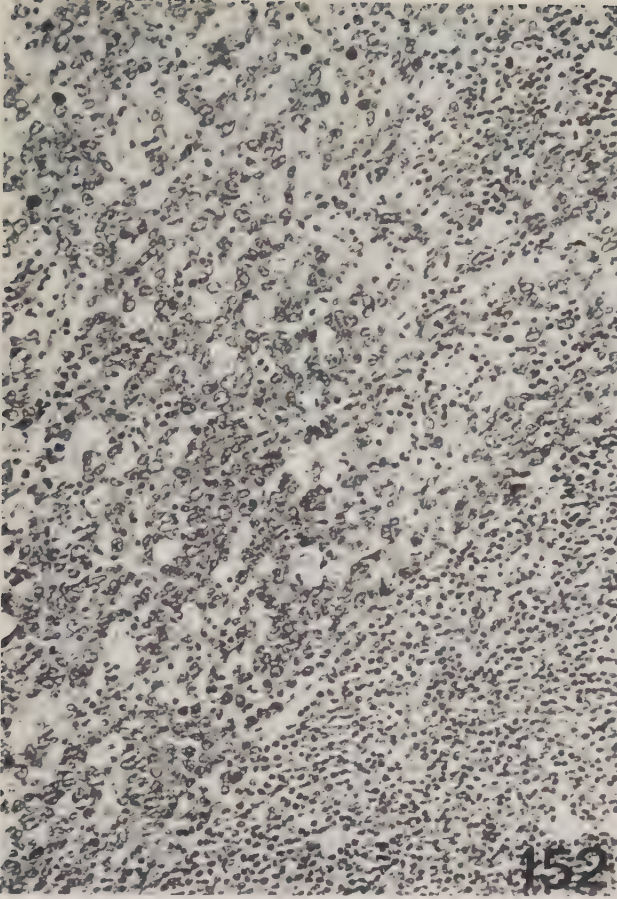


Fig. 156. Electron micrograph of tumour seen in fig. 152. At the bottom of the field a dead cell being phagocytised. The other cells in the field are vital tumour cells. The nuclei have some general resemblance to those of IF-cells but are larger and more irregular. x 5500.

Fig. 157. Nucleus of HL-cell of case 829/69. Two nuclear lobes are connected by a thin bridge. Many nuclear pockets. x 55,000.

Fig. 158. Higher magnification of HL-tumour of case 829/69. Cell in lower right part of the picture is practically identical with IF-2 cell. The other cells in the field are larger and have irregular nuclear contour. Note large amount of granular endoplasmic reticulum. x 7000.

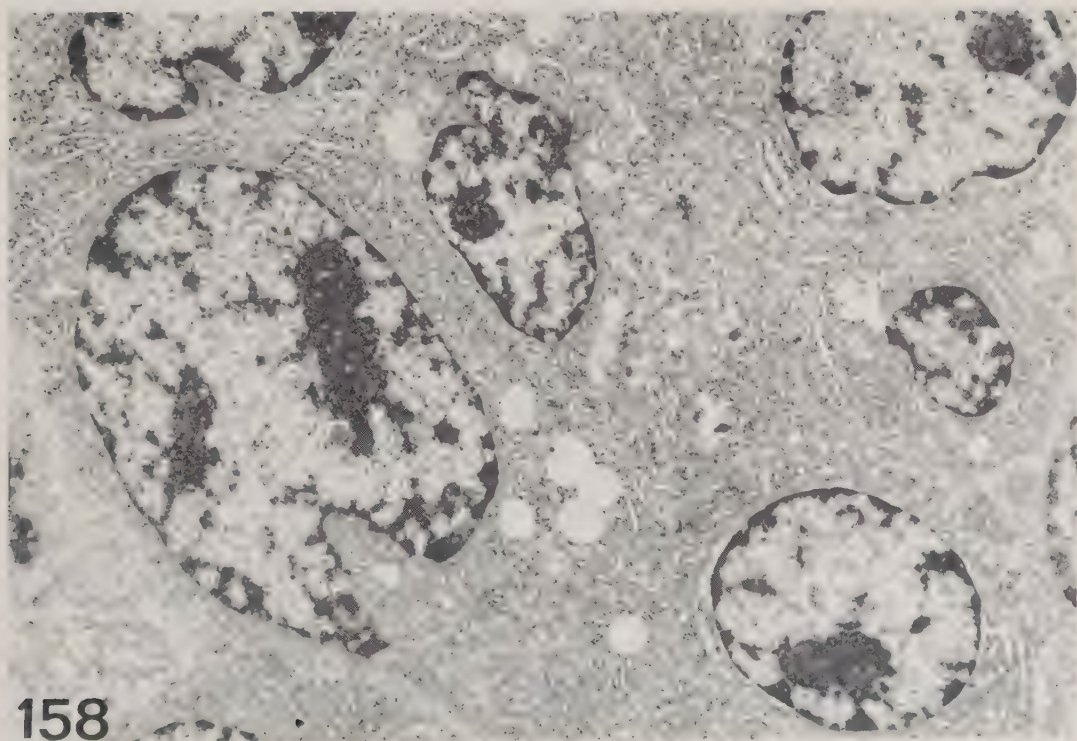
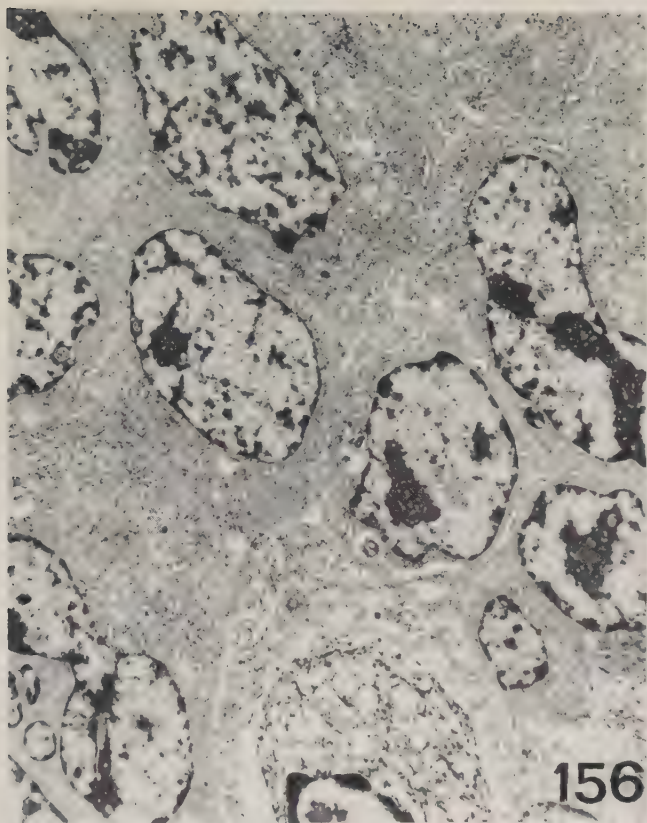


Fig. 159. Mitotic figure in tumour cell of HL in case 829/69. The cell is closely associated with extracellular material of moderate electron density in lower part of the picture. This material is similar to reticulin but could not be demonstrated in the light microscope by silver impregnation. x 5700.

Fig. 160. Heavily contrasted field of HL-tumour of case 829/69. Electron dense material surrounding individual tumour cells and their processes. Within the amorphous material collagen-like fibrils are embedded. x 8400.

Fig. 161. Hyaline, PAS-positive, cytoplasmic inclusion in lymphocytic cell of lymph node biopsy of case 258/68 (LLD-1). This cell was found in the 3rd section after a search in two negative sections. A rough estimation of the number of negative cells examined before a positive cell was found amounts to 200,000. PAS, x 1120.

Fig. 162. Same section as fig. 161. One PAS-positive intranuclear inclusion was also found in this section. PAS, x 1120.

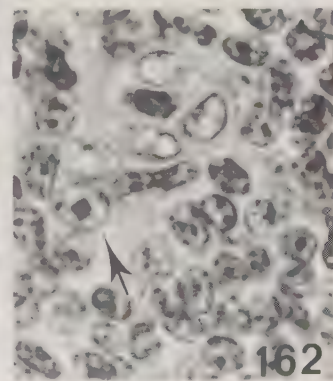
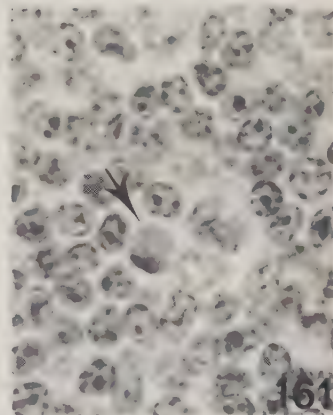
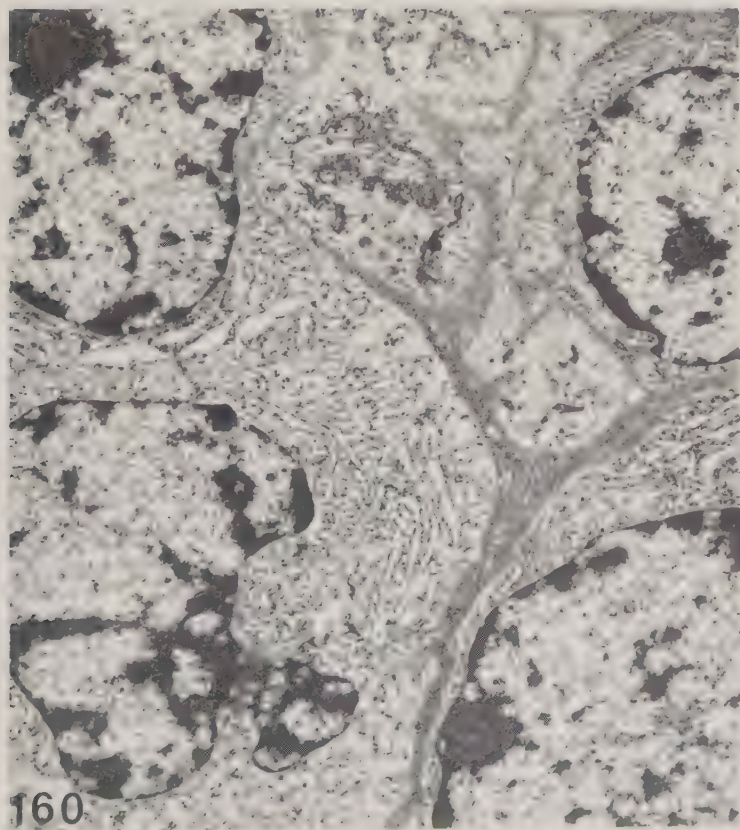
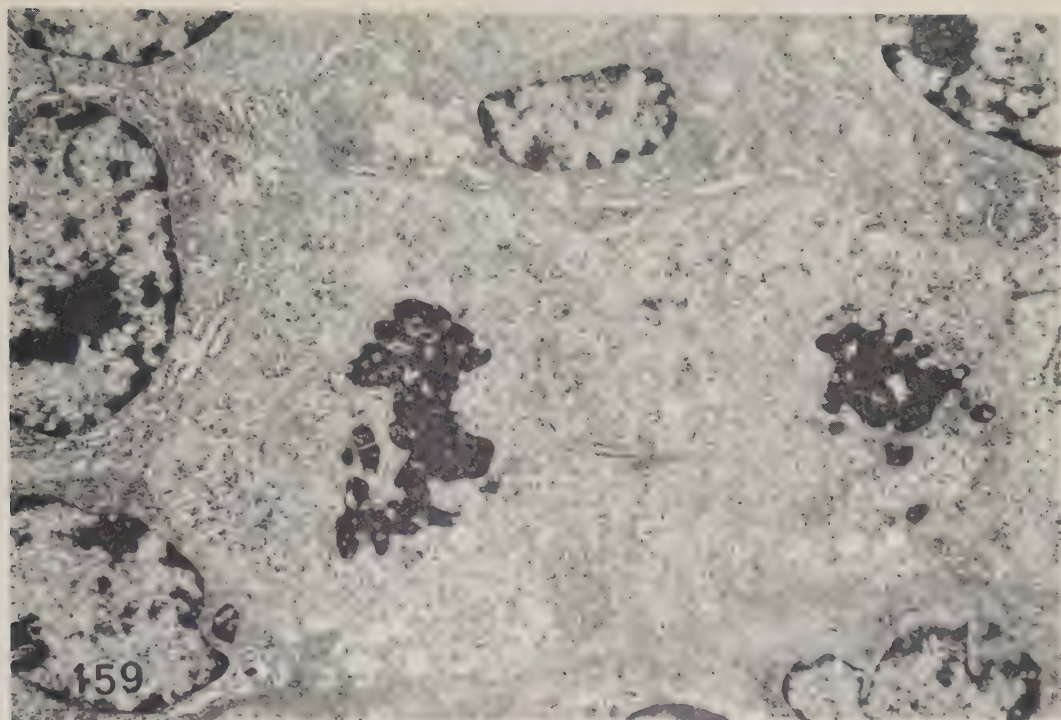


Fig. 163. Bone marrow picture in case 655/63 (LLD-2) at time of the diagnosis. Many prolymphocytes.

Fig. 164. Case 655/63 (LLD-2). Blood picture at time of the diagnosis.

Fig. 165. Bone marrow picture in necropsy specimen of case 655/63. Fibrosis of stroma with prolymphocytic infiltration. x 450.

Fig. 166. Border of HL-lesion in axillary lymph node of case 655/63 (LLD-2). Prolymphocytes and HL-cell. x 1120.

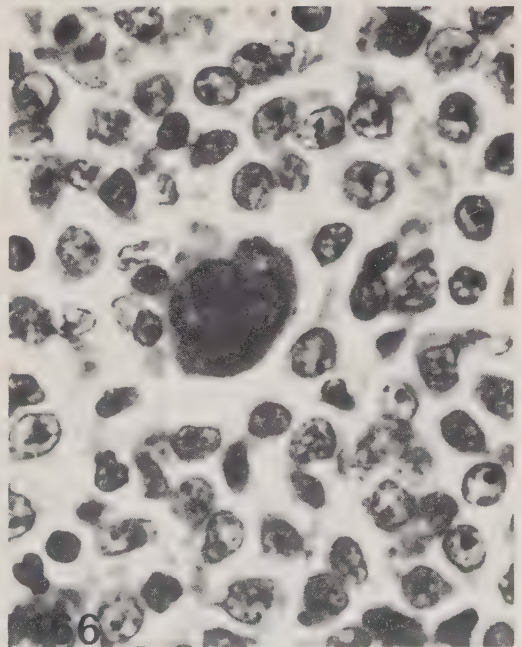
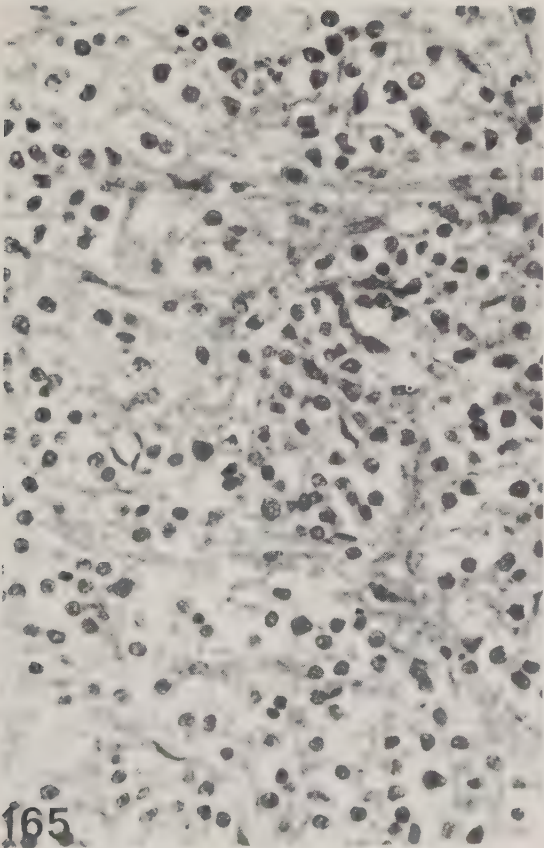
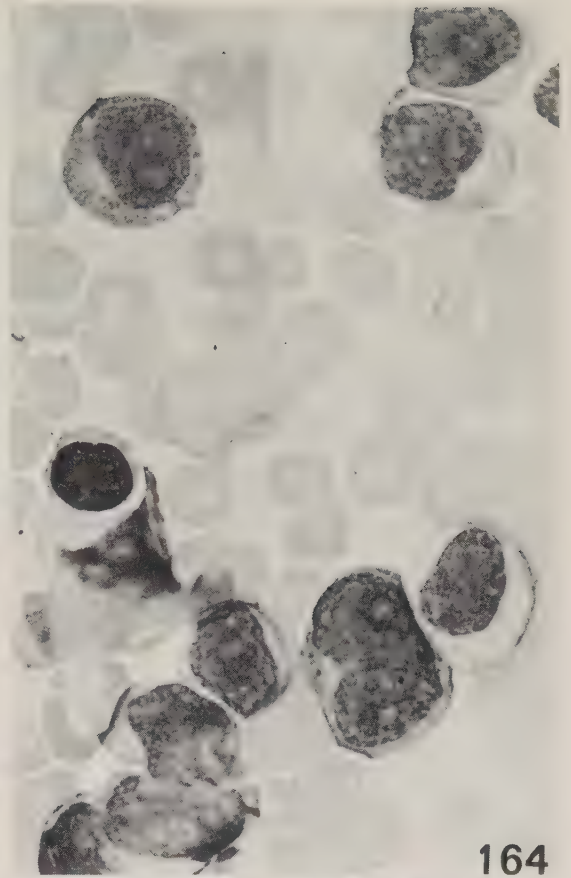
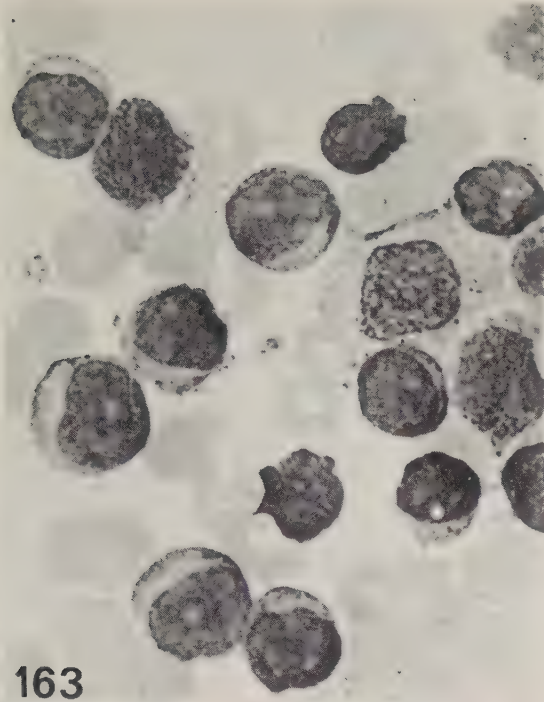


Fig. 167. Axillary lymph node of case 655/63 (LLD-2) demonstrating central HL-focus compressing surrounding lymphocytic parenchyma. x 15.

Fig. 168. Higher magnification of HL-tissue in fig. 167. x 180.

Figs. 169 and 170. High power fields of fig. 168. x 1120.

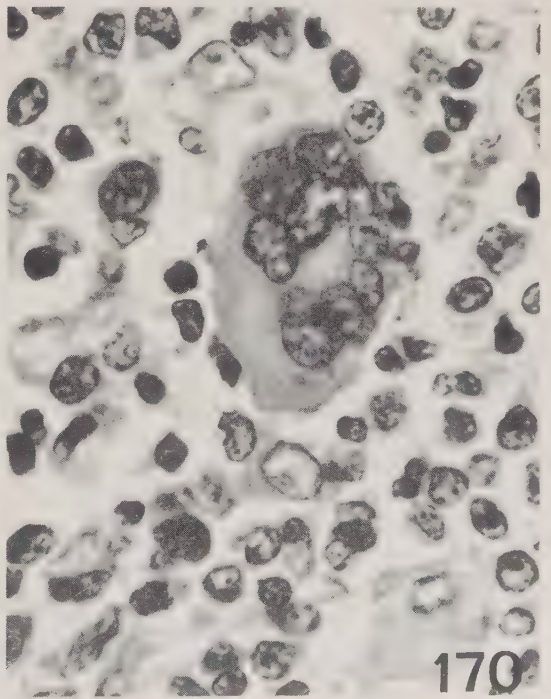
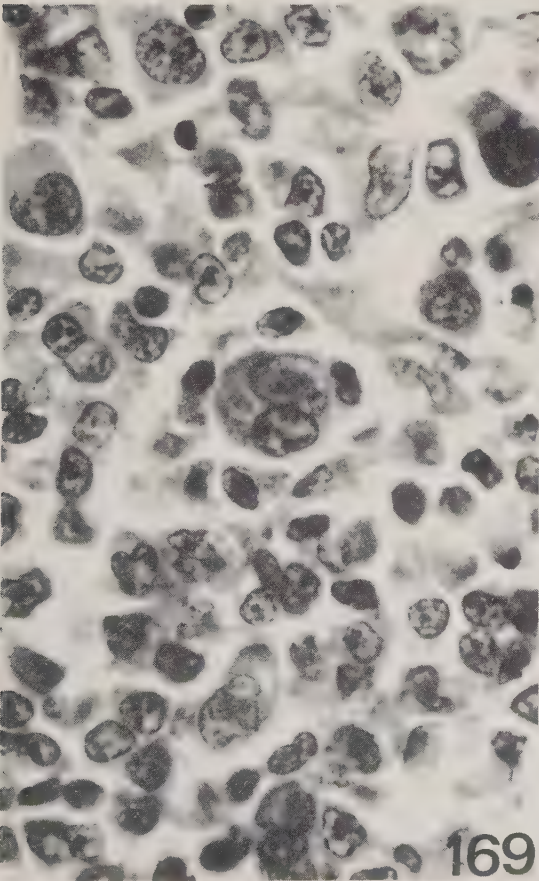
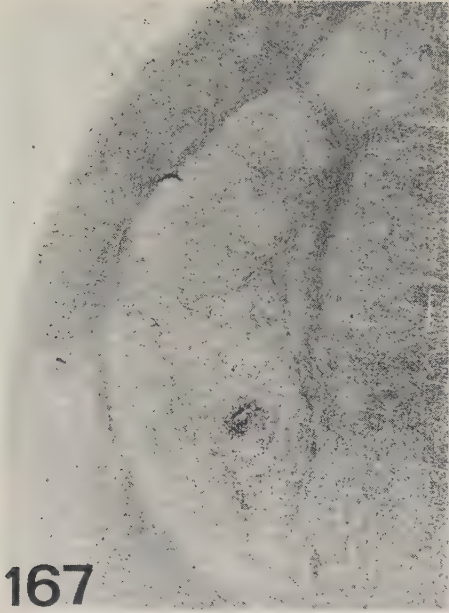


Fig. 171. Lymph node biopsy of case 855/67 (LLD-3). This "cloudiness" is sometimes seen in LLD-3 and may be called nodular according to Rappaport. But the tumour nodules do not resemble true follicles. Such "cloudiness" has not referred a case to nodular lymphoma in this work. x 35.

Fig. 172. High power view of fig. 171. Predominantly mature lymphocytes, but many atypical. x 1120.

Fig. 173. Necropsy specimen from HL-tumour in liver from case 855/67. Immunoblastic type of HL, x 450.

Fig. 174. High power view of fig. 173. Multinucleated tumour cell with giant nucleoli, somewhat resembling Reed-Sternberg cell. x 1120.

Fig. 175. Necrotising arteritis in HL-tissue from case 855/67. x 170.

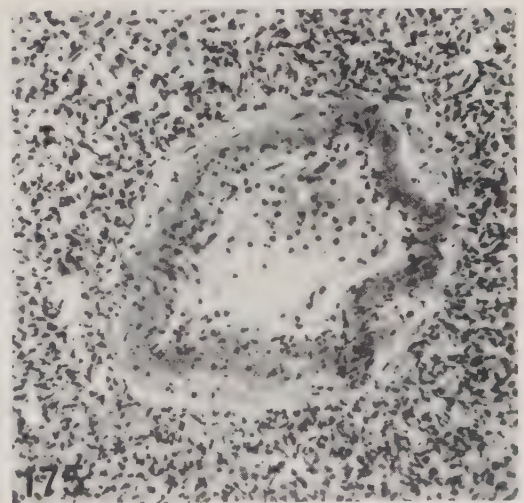
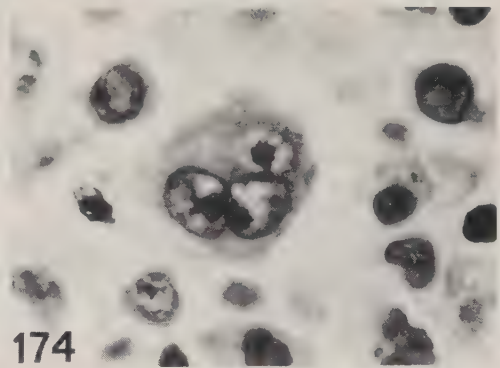
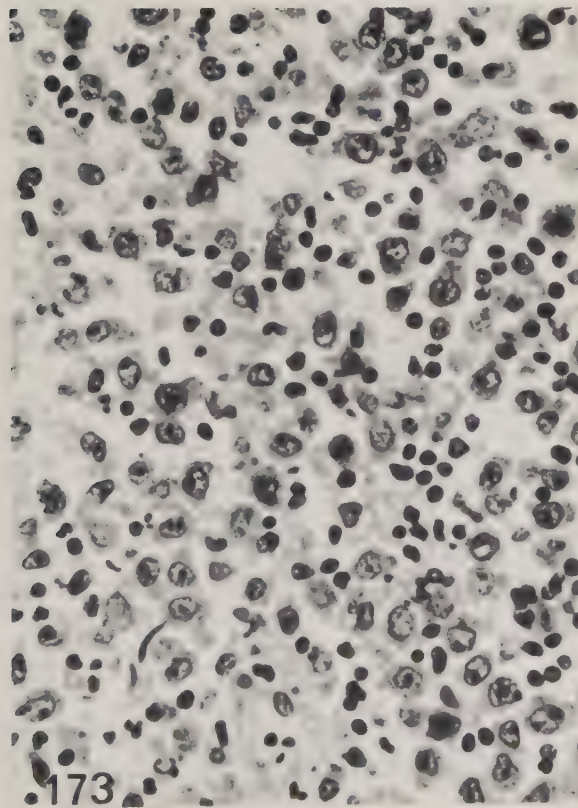
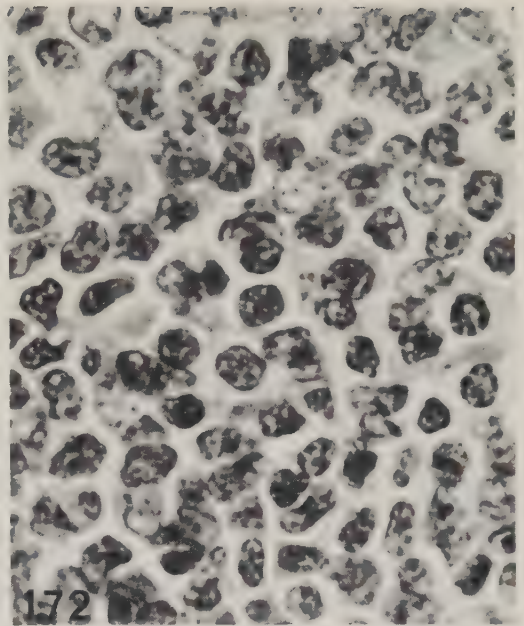


Fig. 176. Case 290/70 (LLD-3). Section of necropsy specimen of bone marrow, showing lymphocytic infiltration. x 1120.

Fig. 177. Case 290/70. HL in nasal polyp at time of diagnosis. Compare picture of bone marrow in fig. 176. x 1120.

Fig. 178. Case 290/70. Fine-needle aspirate of cervical lymph node affected with same tumour as in fig. 177.

Fig. 179. Example of HL developing terminally in LLN (case 609/69). The tumour cells resemble those of HL following LLD-1, -2 or -3. But the cells are often more variable in size and shape and have smaller nucleoli. But no clear histologic boundaries between the two types. x 1120.

Fig. 180. Fine-needle aspirate from lymph node illustrated in fig. 179. The cytologic appearance is very similar to that in fig. 178, for example.

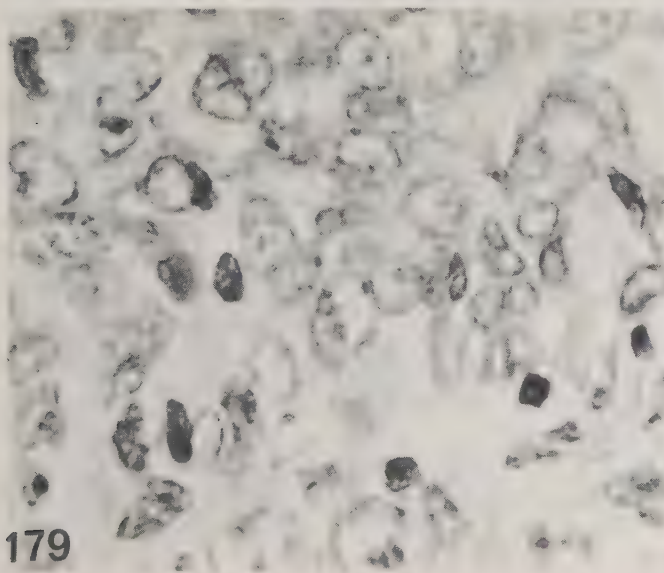
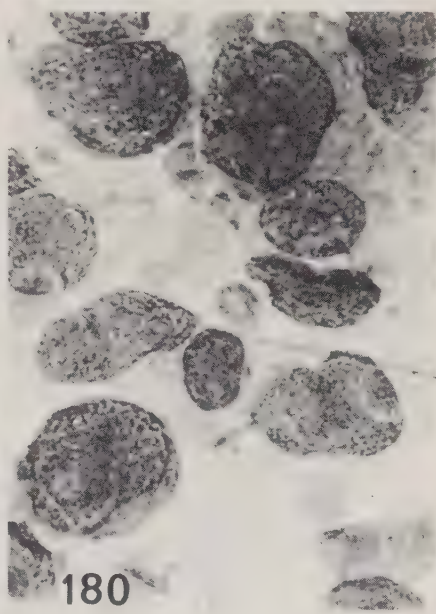
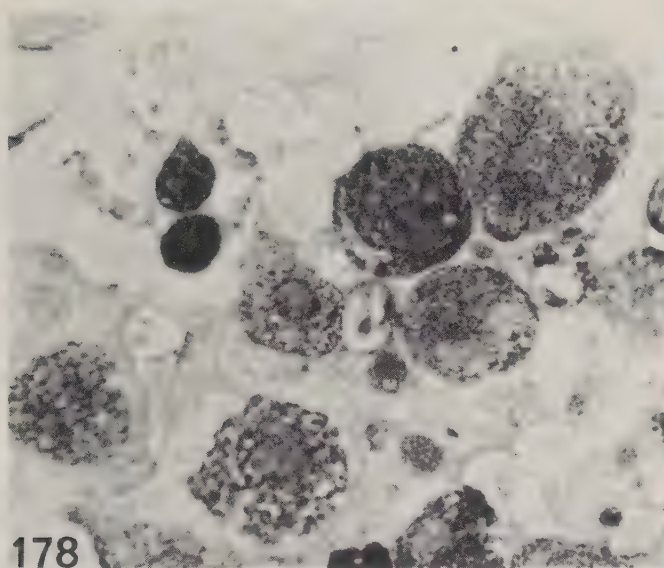
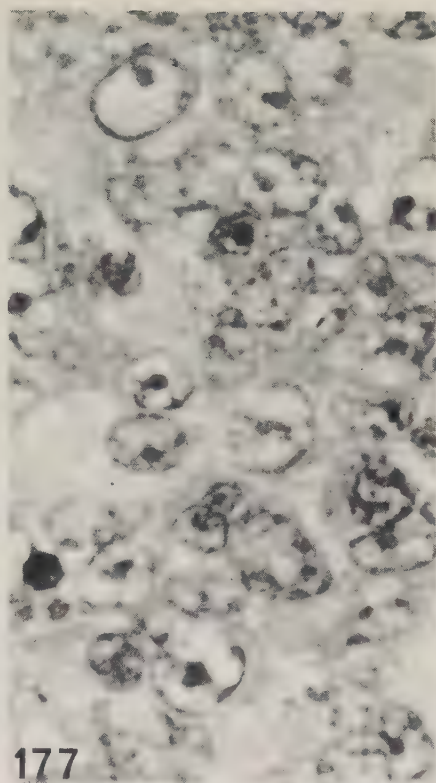
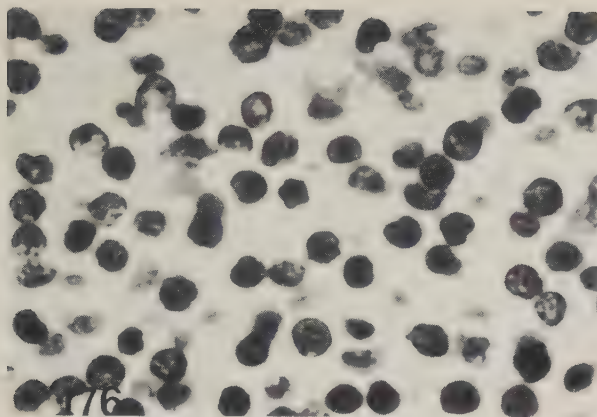


Fig. 181. LLD-1. Lymph node biopsy of case 2-219. Large, partly coalescent IF. This field was selected for electron microscopy. x 210.

Fig. 182. High power view of large IF. IF-1 cell at asterisk. Some IF-2 cells in centre of picture (arrow points to typical example). Arrow is situated on a macrophage, whose nucleus is poorly stained with Giemsa. A small vessel is seen (top centre). Most of the cells in the field are prolymphocytes. Giemsa, x 1300.

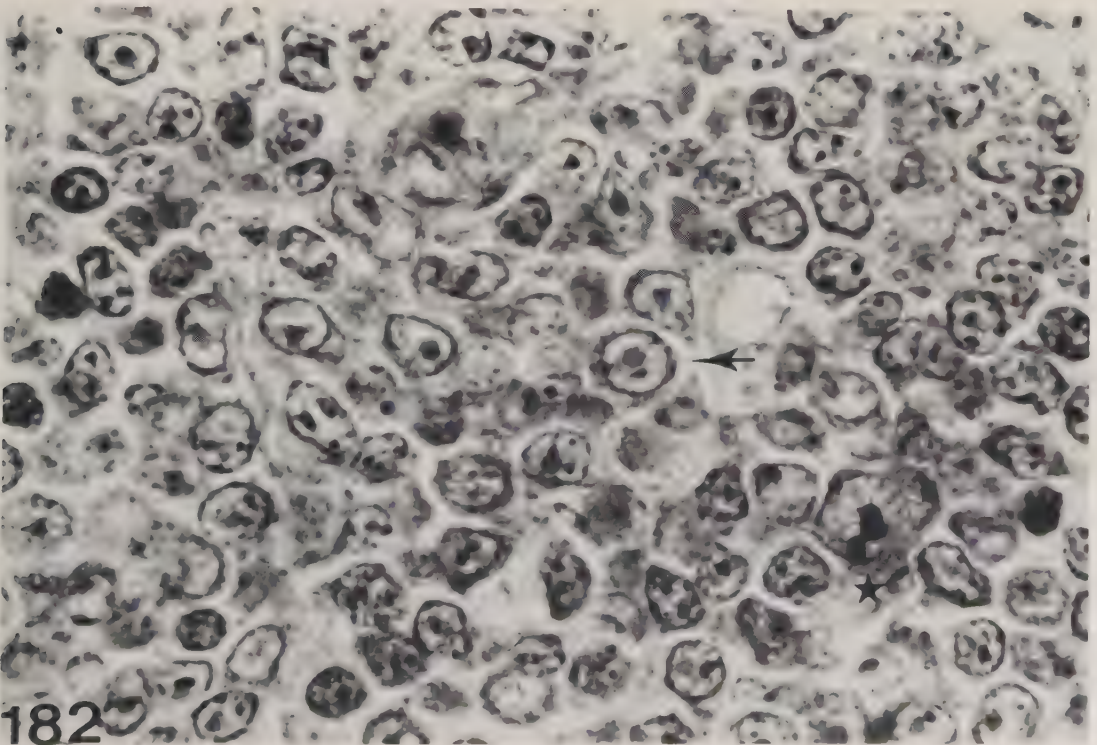


Fig. 183. Electron micrograph of IF. The large cell in top centre position is a typical IF-2 cell. In the right lower corner is a mitotic figure in another IF-2 cell. In the centre of the field some mature lymphocytes. Most other cells in field are prolymphocytes. Arrows point to typical examples. Reticulum fiber at thick arrow. x 3900.

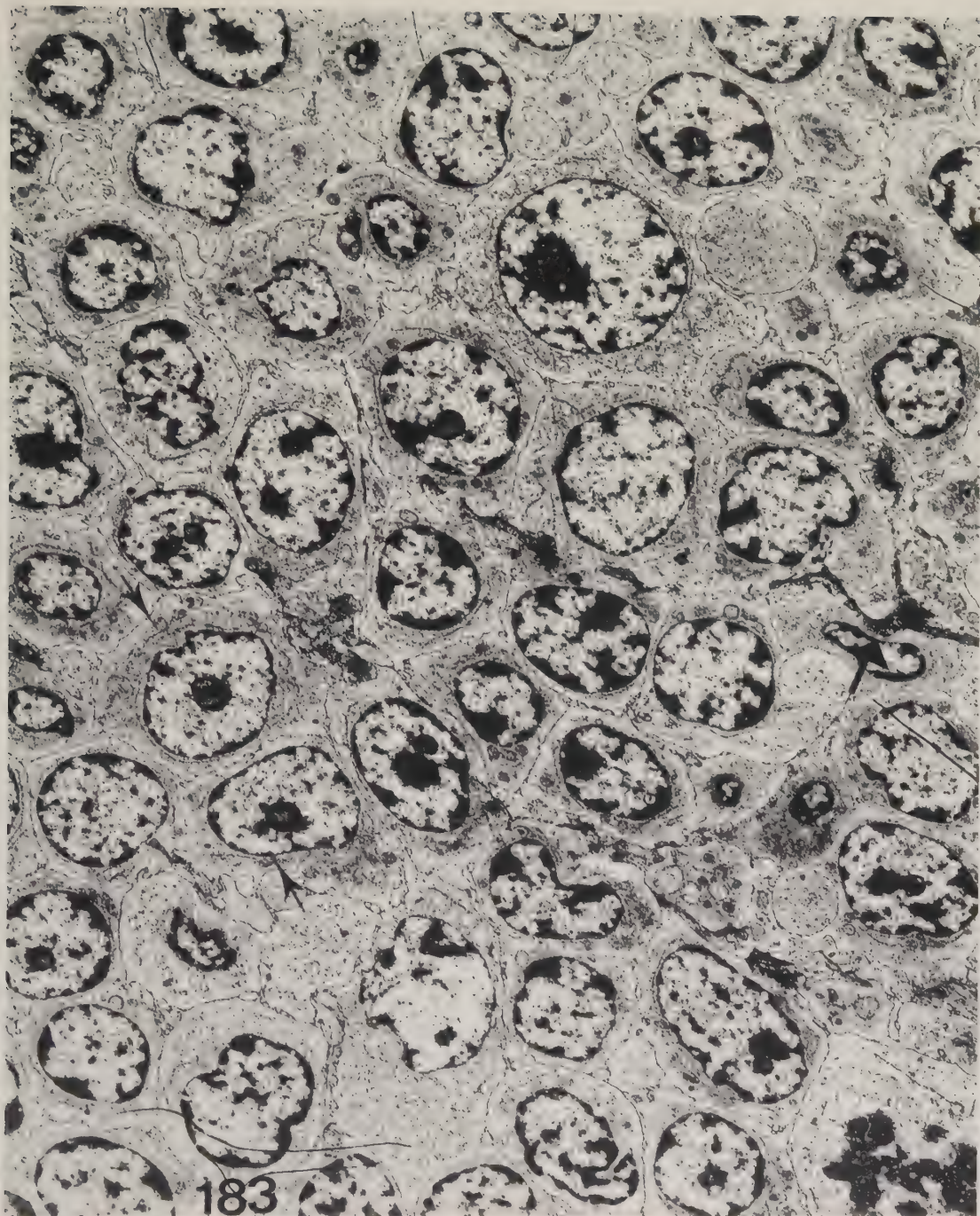


Fig. 184. An IF-2 cell with a tapering process in upper part of the picture (asterisk). A macrophage to the right of this cell. In lower part of reproduction two reticulum cells. They have tortuous processes connected by desmosomes (arrow). x 7000.

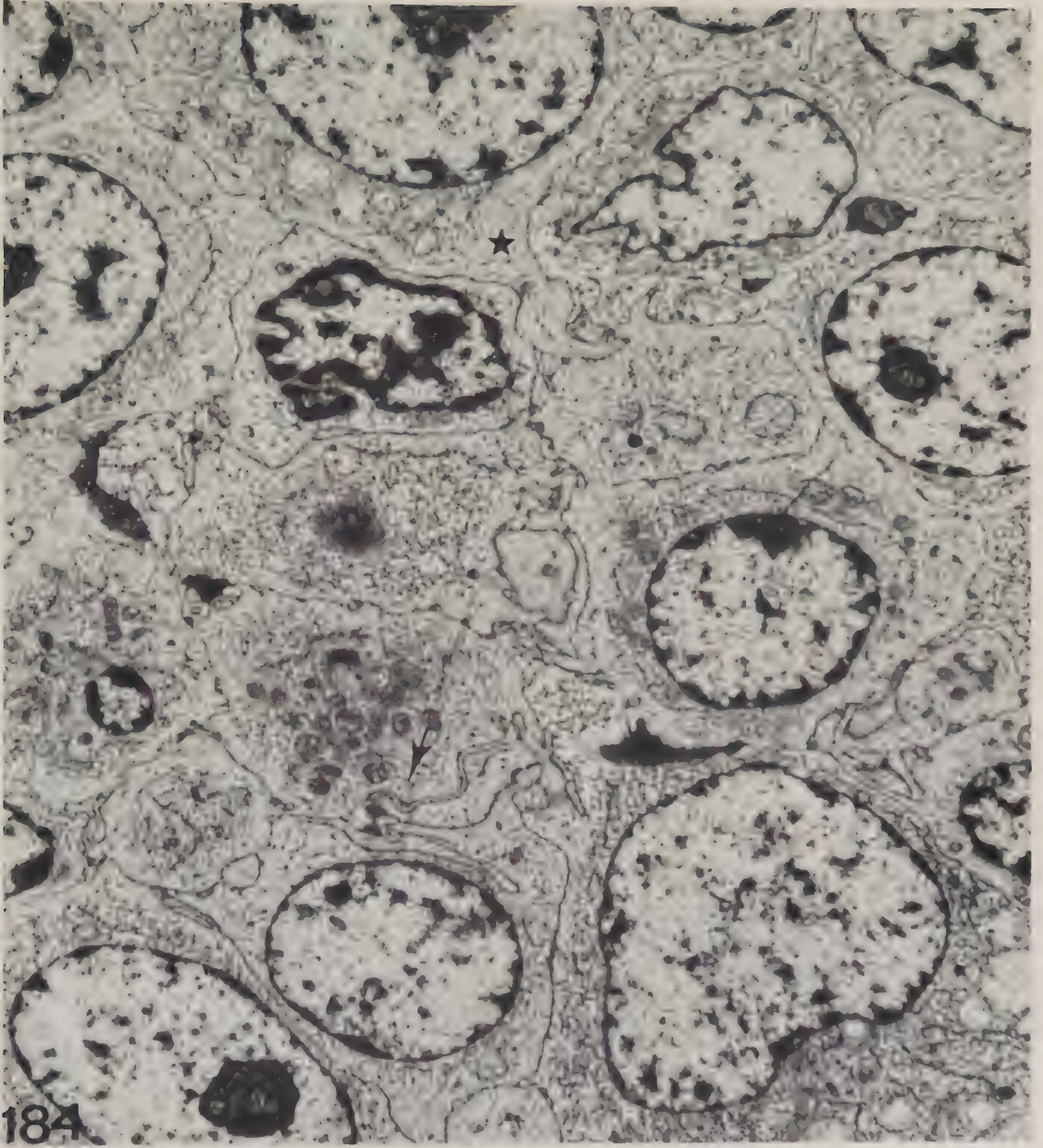


Fig. 185. The process of the IF-2 cell of fig. 184 in higher magnification. A bundle of tubules at arrow. Fine filaments running obliquely to cell surface. At tip of the process is a desmosome, not ideally oriented to the plane of section. Highly complicated surface interrelation of cells. x 46,000.

Fig. 186. Higher magnification of connections between reticulum cell processes seen in fig. 184. Two desmosomes. x 25,000.

Fig. 187. Another cell process with desmosomal connections (this process is seen in the right part of fig. 184). It is impossible to know whether such a process stems from a reticulum cell or an IF-2 cell. x 31,000.

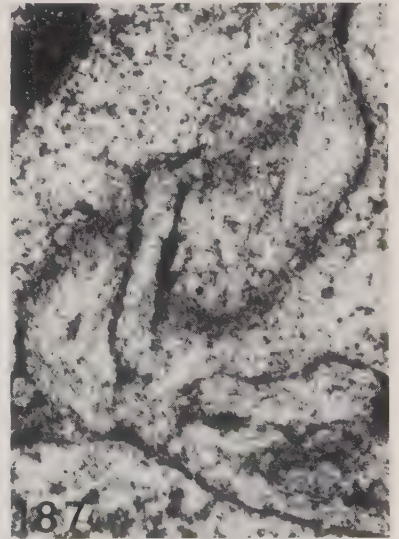
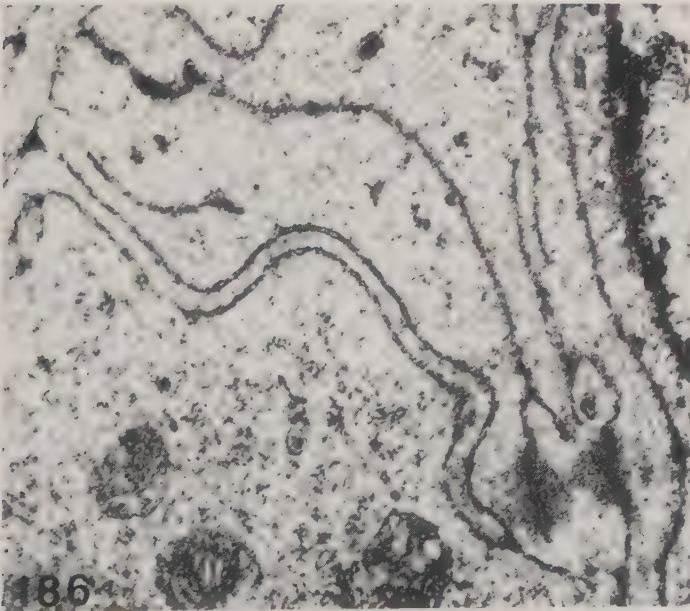
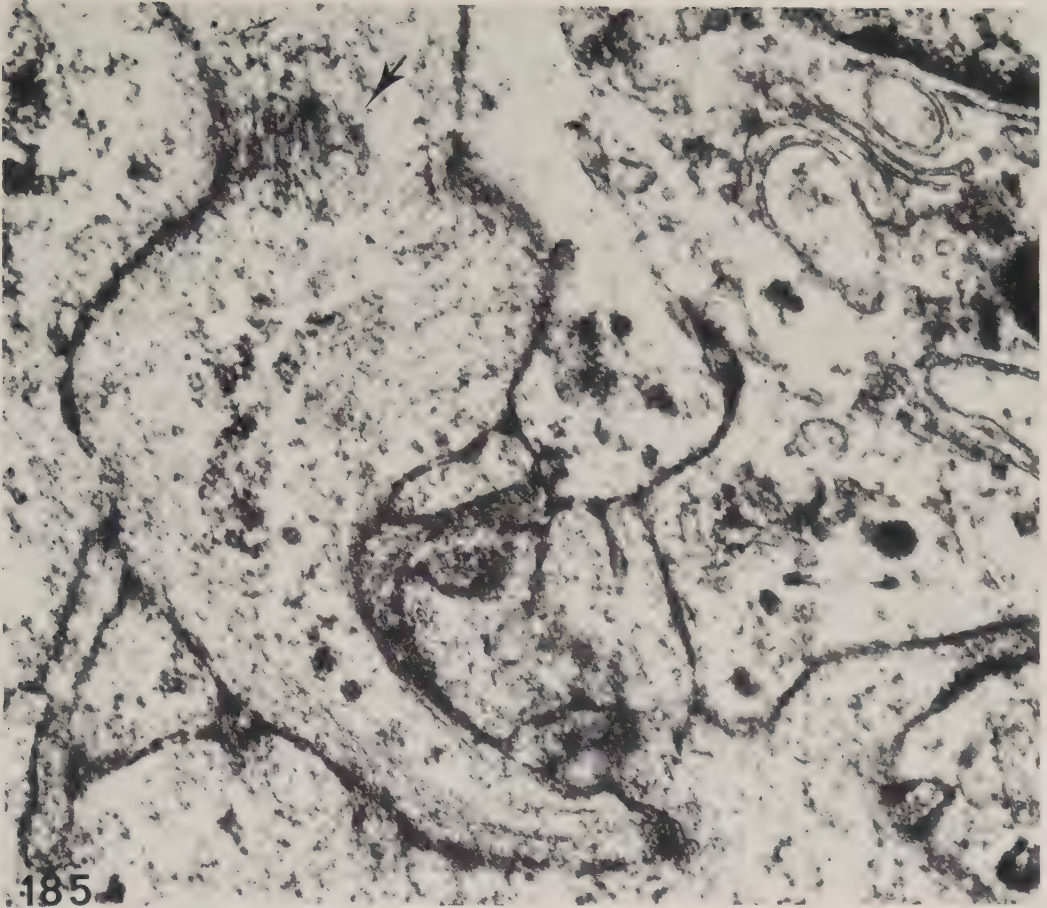


Fig. 188. An IF-1 cell. Somewhat irregular nuclear contour, many large nucleoli, cytoplasm poor in organelles except for many polyribosomes. x 11,000.

Fig . 189. A lymphocyte to the left, to the right an IF-2 cell with a bifurcated process. This cell is not sectioned through its largest diameter, but also at that level the cell was considerably smaller than the IF-1 cell. Compare size of IF-1 cell in fig. 188 (same magnification). x 11,000.

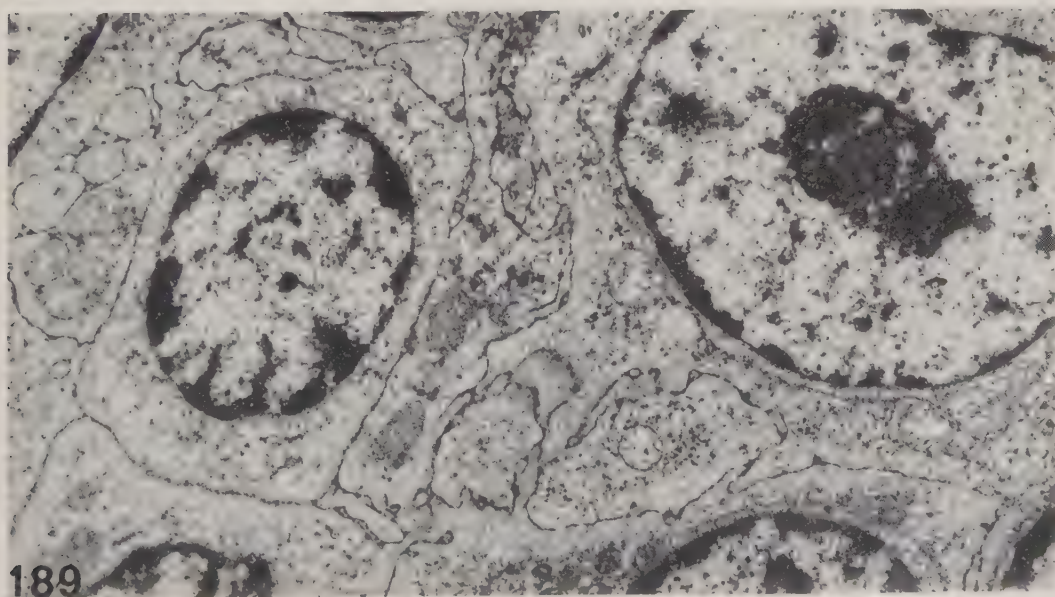
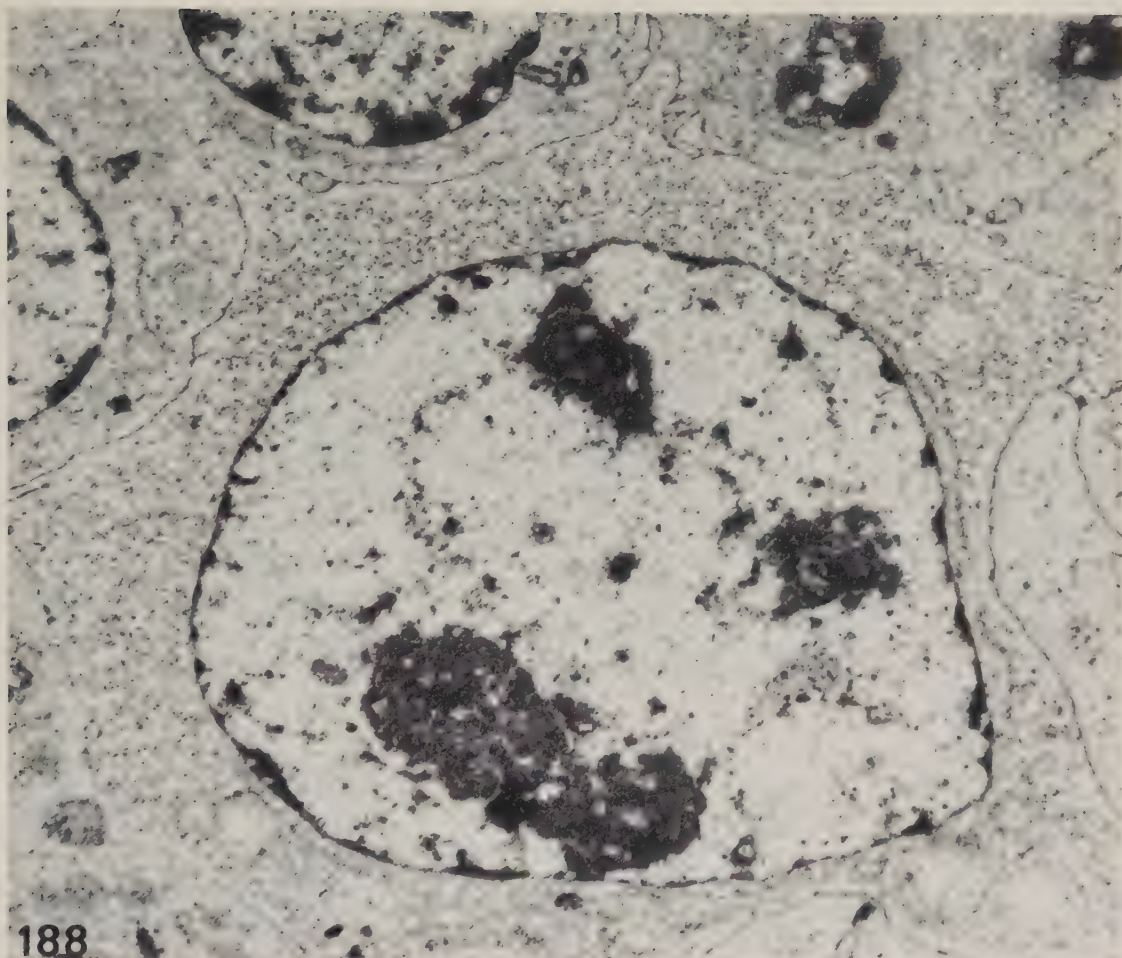


Fig. 190. To the left an IF-1 cell, to the right an IF-2 cell, in the middle an IF-3 cell. Cell sizes not strictly comparable because of sectional effects. The IF-3 cell has a long, tapering process towards the right. Many wavy fibrils to the right of the nucleus. Several reticulum fibres. The IF-3 cell shows a desmosome at the arrow (not well visible in this magnification). x 5400.

Fig. 191. An IF-2 cell to the left, an IF-3 cell to the right. Note difference in density of cytoplasmic organelles and somewhat different appearance of the granular endoplasmic reticulum. x 12,000.

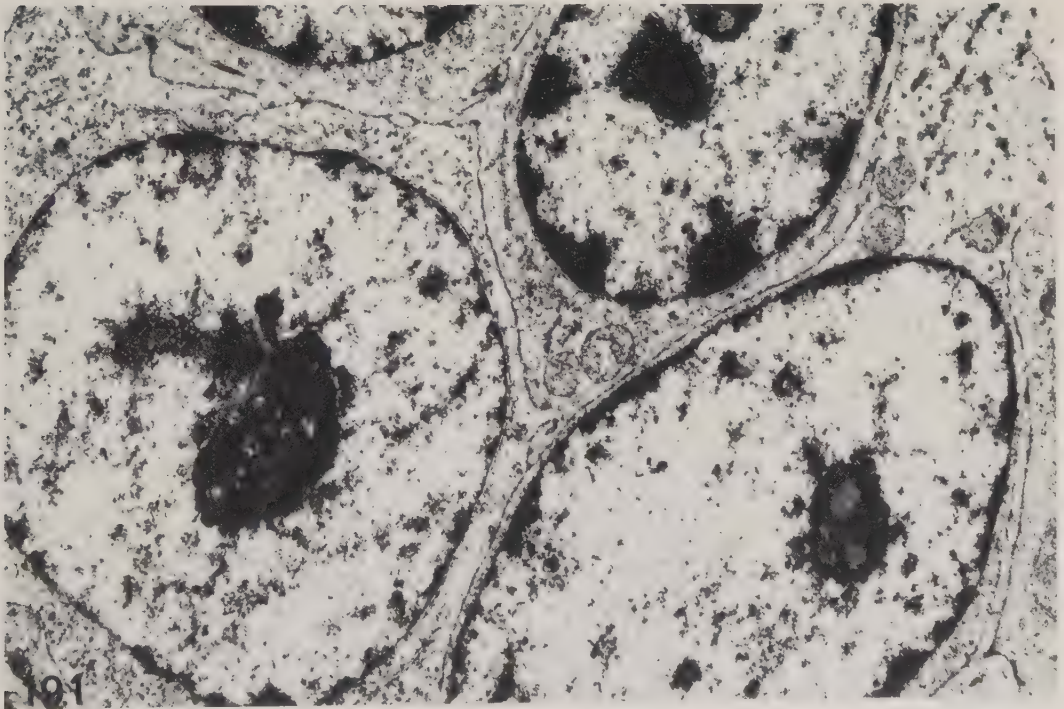
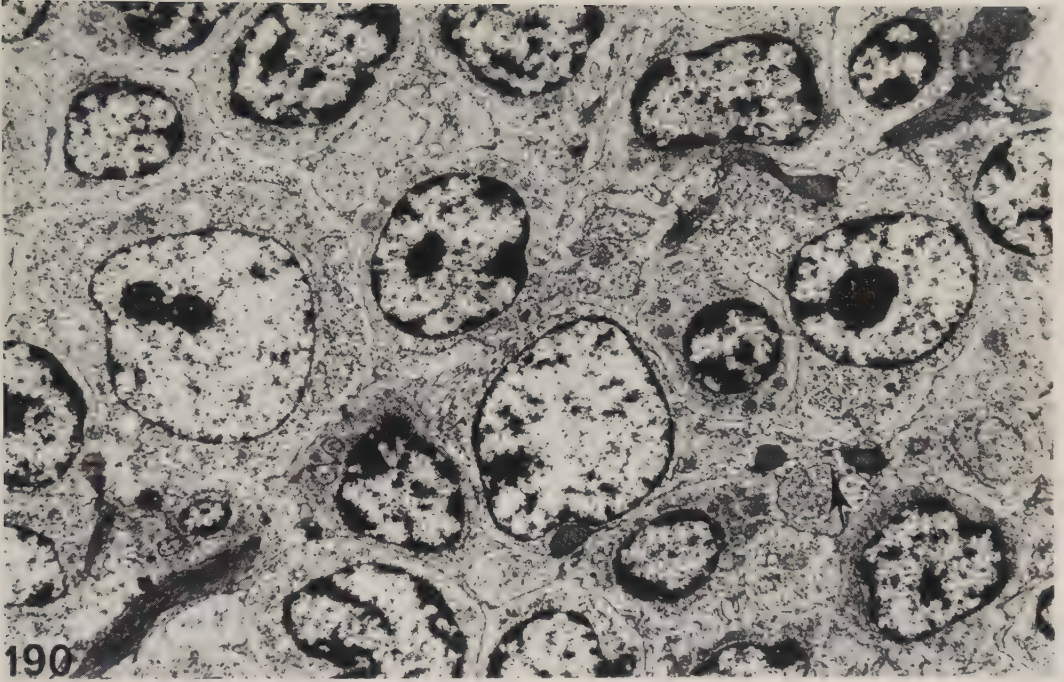


Fig. 192. Elongated cell, intimately associated with reticulum fibre. The cytoplasm resembles that of IF-3 cells, the nucleus has no visible nucleolus in this plane. It is not possible to know whether this is an IF-3 cell or a fibroblastic reticulum cell. x 6600.

Fig. 193. Gall-body like structure in process from IF-3 cell (centre). Similar structures in prolymphocytes to the right and above. x 18,500.

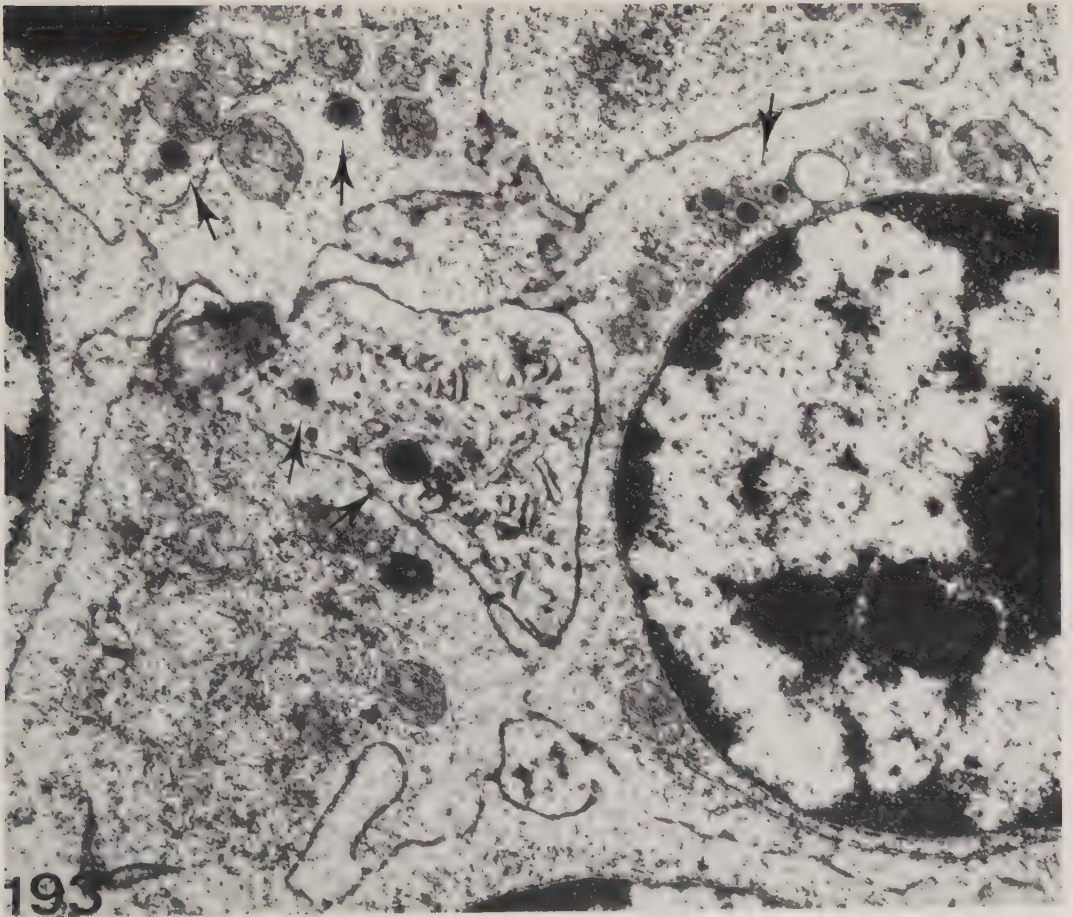
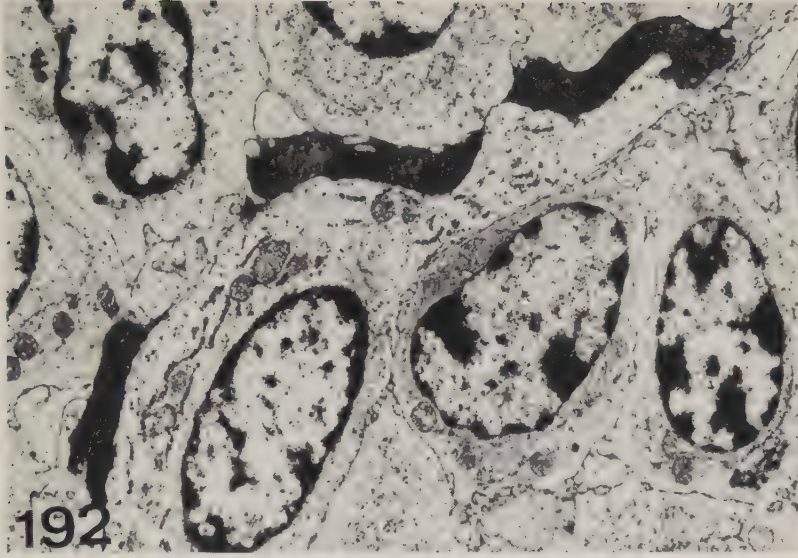


Fig. 194. IF-2 cell in mitosis. Note whorl of granular endoplasmic reticulum. Gall-body like granules at arrows. Vacuolisation of mitochondria is due to poor fixation. x 12,500.

Fig. 195. A "dark cell" with very long processes, winding in and out of the section. Nucleus in lower left corner, winding and branching process arrowed. x 8500.

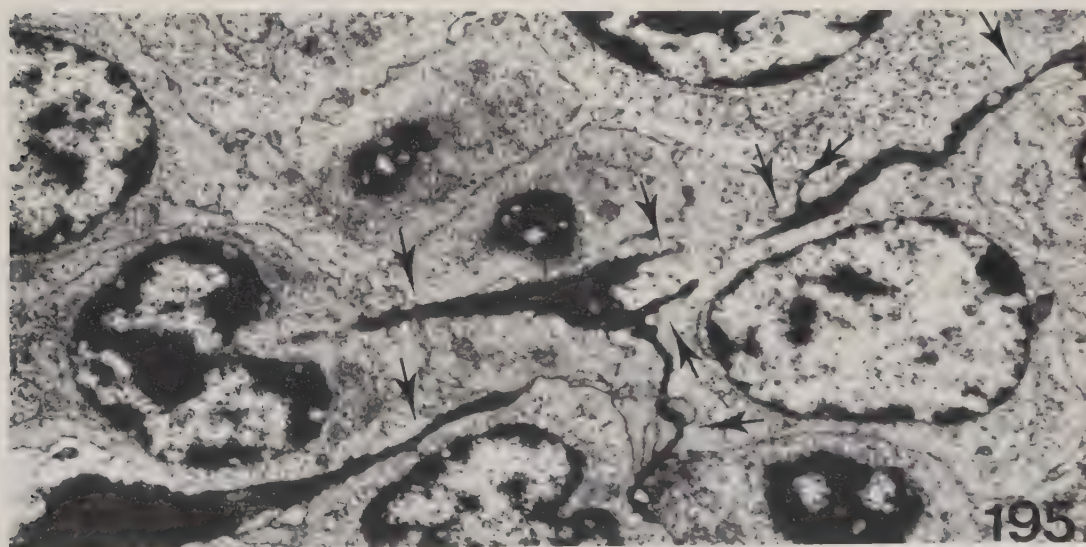
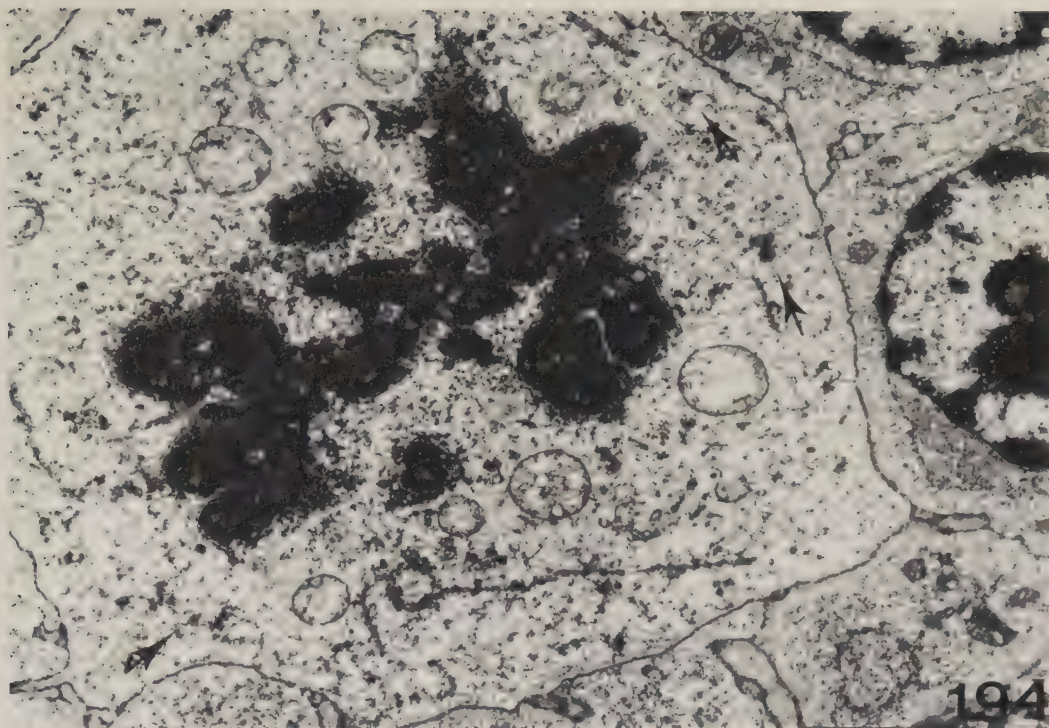


Fig. 196. Desmosomal connection between two IF-cells. Note the highly winding and complex surface interrelationship between the cells. In many places fine filaments are seen in a peripheral position in the cell, seemingly inserting in the plasma membrane. x 30,000.

Fig. 197. Higher magnification of desmosome in fig. 196. This type of desmosomal attachment was seen most often. A short, slightly bent process from a cell has a desmosomal attachment on its side to the body of another cell. Fine filaments seem to insert in the desmosome within the process. These filaments pass for a short distance into the body of the cell. At the origin of the process from the cell body there sometimes appears to be an annular structure. Ideally oriented desmosomes were very hard to find, while such as had been sectioned at oblique angles were seen more often. x 67,500.

Fig. 198. Another desmosomal attachment similar to that of fig. 196. x 40,000.

Fig. 199. An annular complex of laminated granular endoplasmic reticulum, similar to such structures as have been described in leukemic reticuloendotheliosis. Such structures were seen in occasional cells, predominantly in prolymphocytes and IF-2 cells. x 30,000.

Fig. 200. A macrophage. The nucleus is contorted, the cytoplasm contains many lysosomal granules of different shape and electron density. The cell has a long "tail". x 6000.

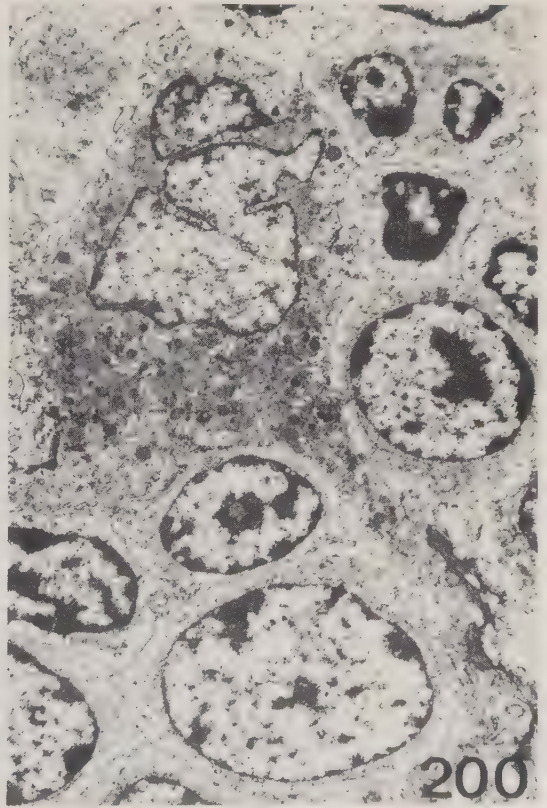
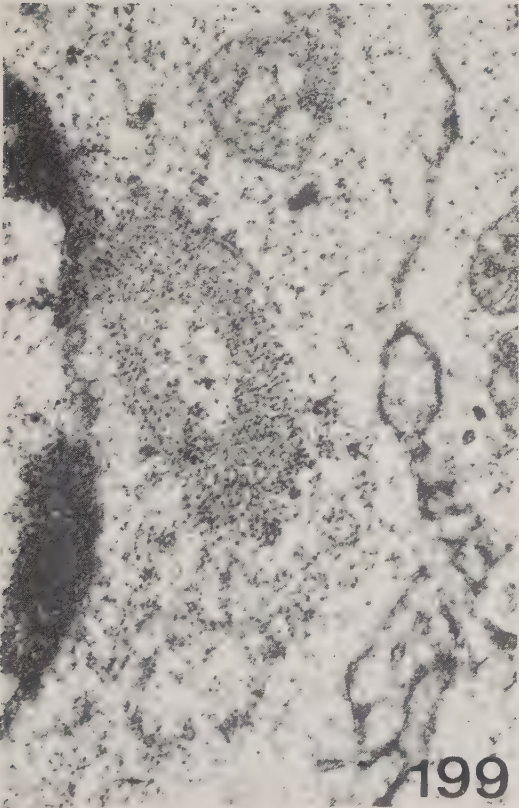
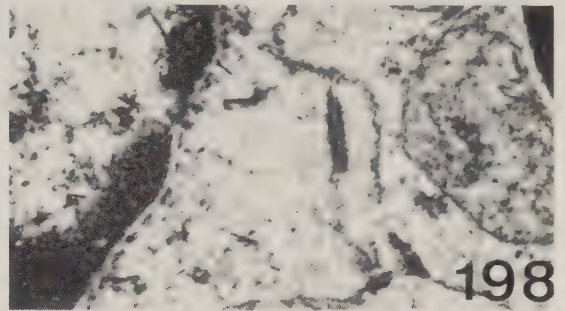
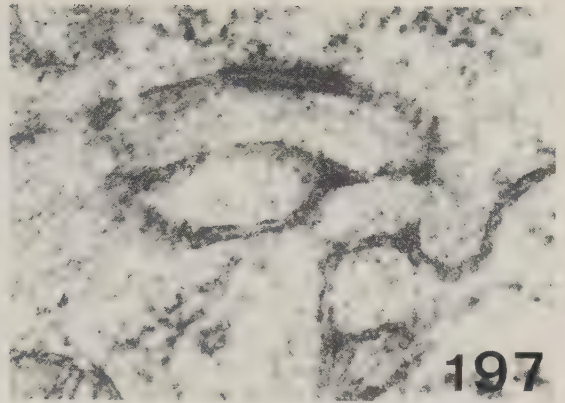
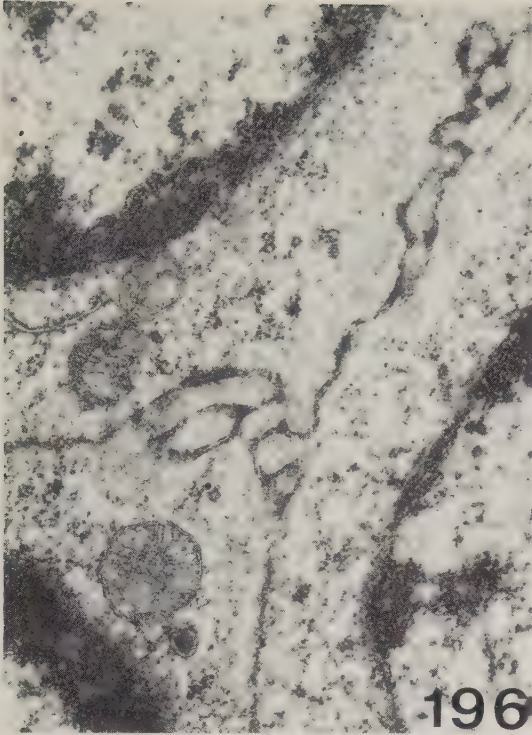


Fig. 201. Rare examples of this cell type were found in case 2-219. The cell is ovoid with a smooth outline without interdigitations. Parallel stacks of granular endoplasmic reticulum surround nucleus (arrow). The cell is similar to an immature plasma cell. x 10,000.

Fig. 202. A prolymphocyte. Gall-body like structure at lower arrow. Some strands of granular endoplasmic reticulum. Two cross-sectioned reticulum fibres are seen close to the cell (asterisks). They are partly ensheathed by processes of a "dark" cell (arrows). x 11,700.

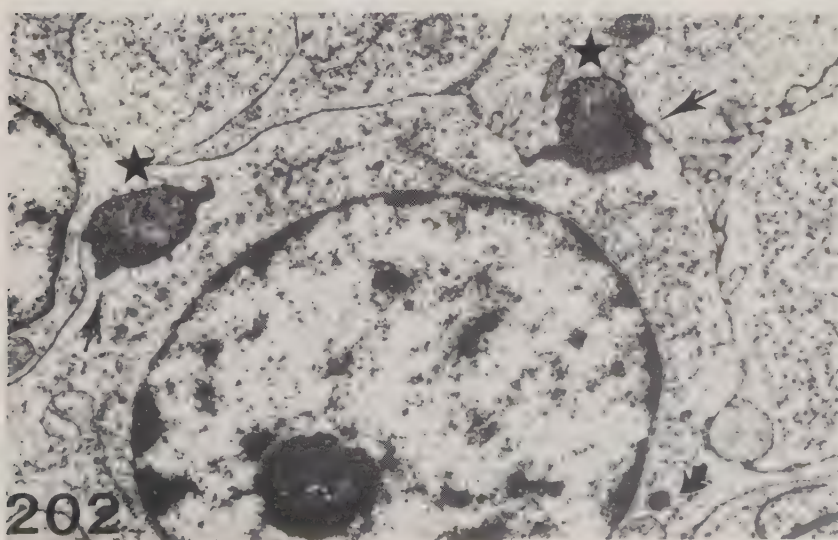
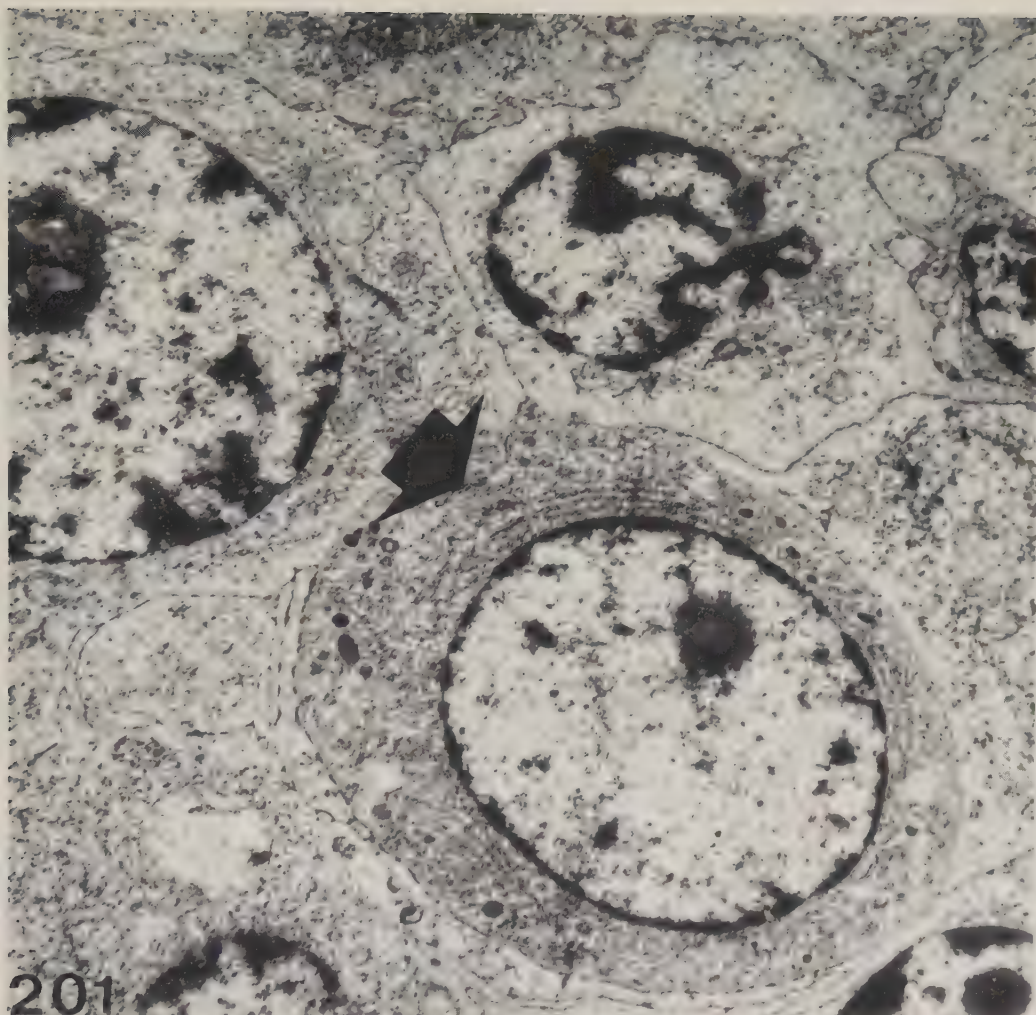


Fig. 203. Group of wavy, thread-like structures in cytoplasm of IF-cell. A membrane bounded body containing polymorphous membraneous material is seen in lower part of the picture. x 60,000.

Fig. 204. Higher magnification of fig. 203. In the lower part of the picture the structures are cross-sectioned, in the upper part they are cut obliquely or along their axis. x 206,000.

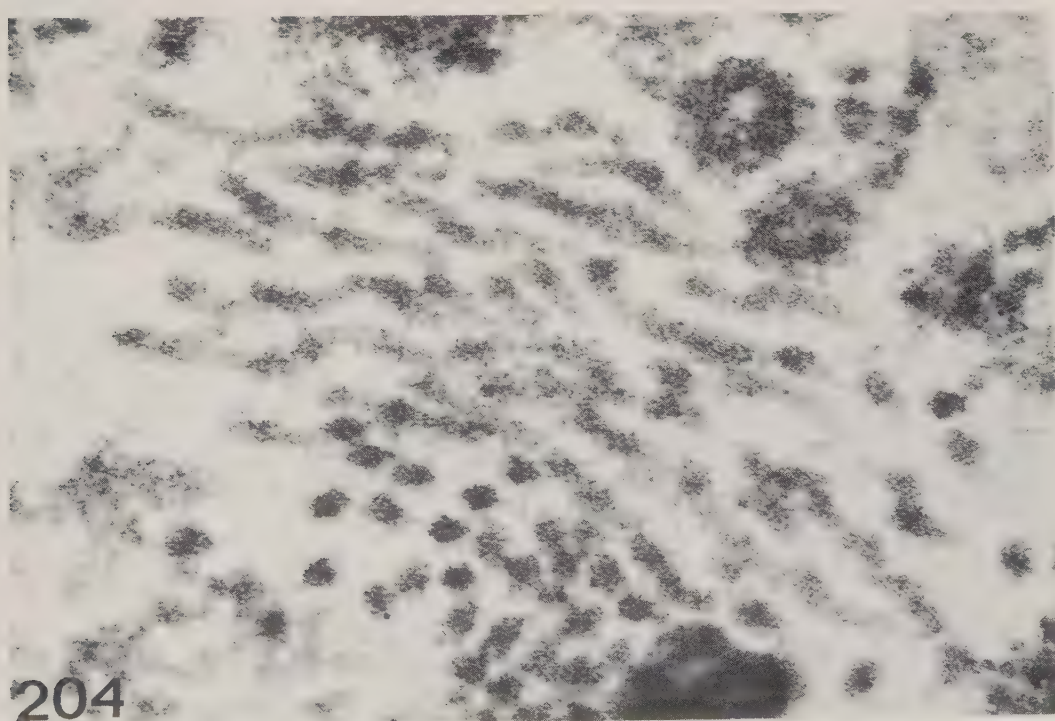
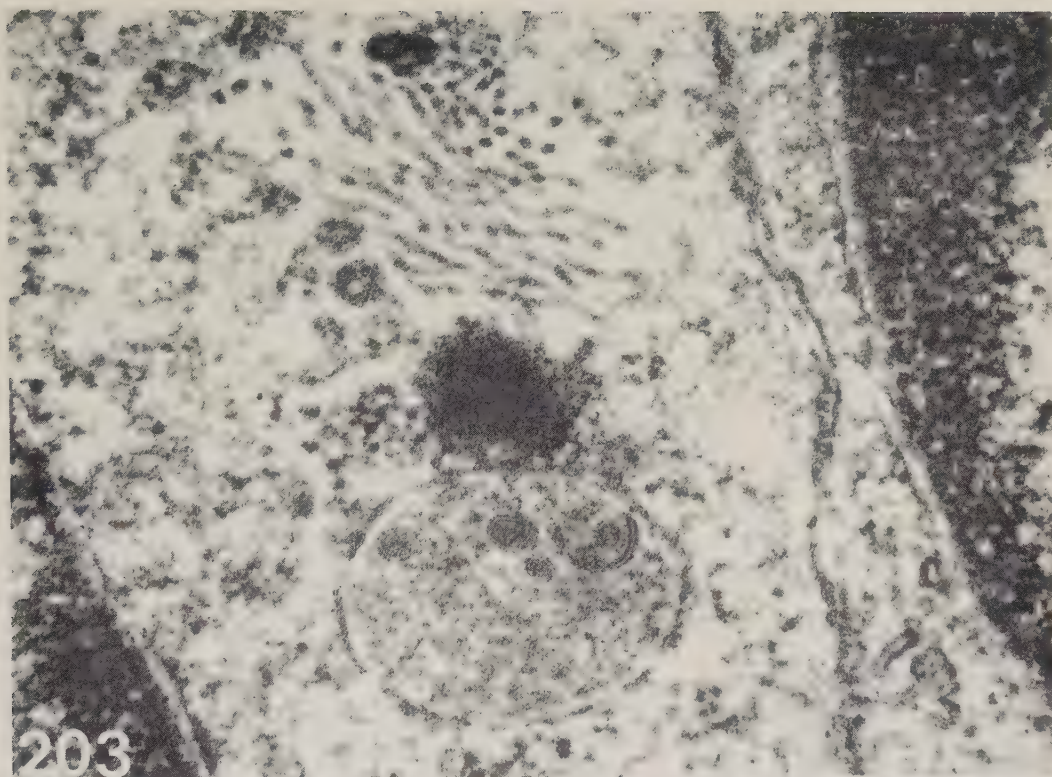


Fig. 205. Light microscopical illustration of high endothelium venule within IF. The wall consists of many lamellae of basal membrane, surrounding pericytes. Lymphocytes are seen traversing the endothelium and within the lamellae of the basal membrane. They travel through gaps in the outermost lamella. Toluidine blue, x 1120.

Fig. 206. Electron micrograph of lymphocyte (arrow) traversing endothelium of high endothelium venule. Another lymphocyte within lumen at top. x 12,000.

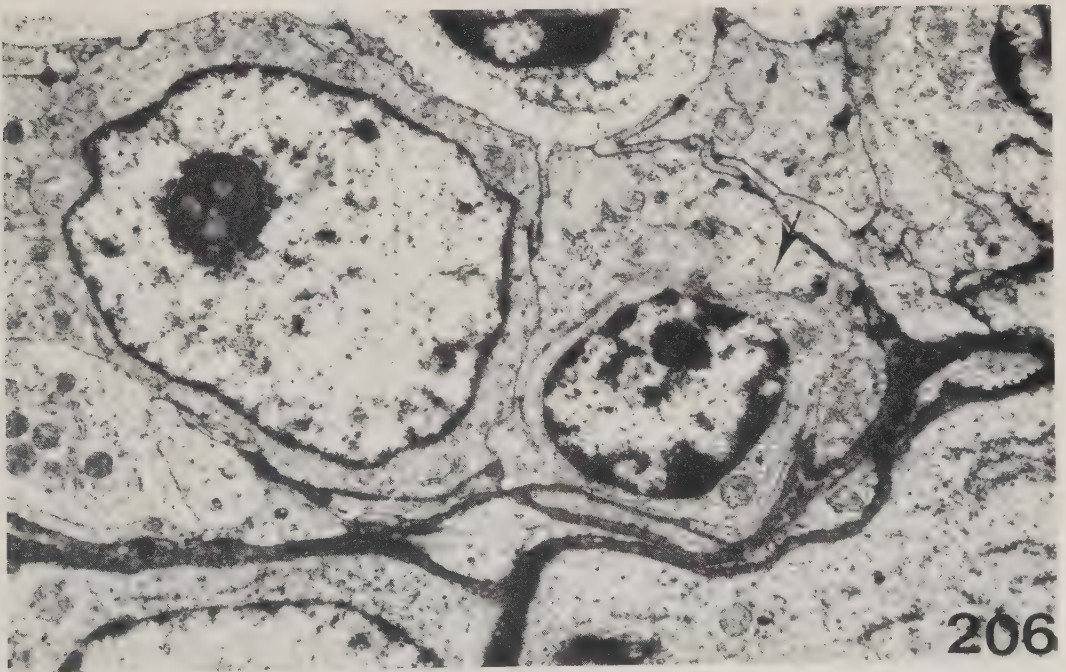
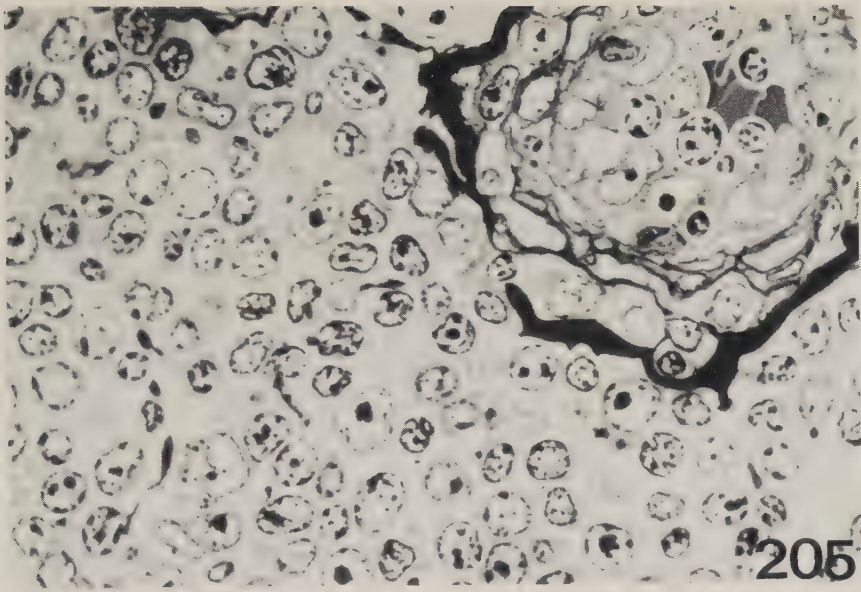
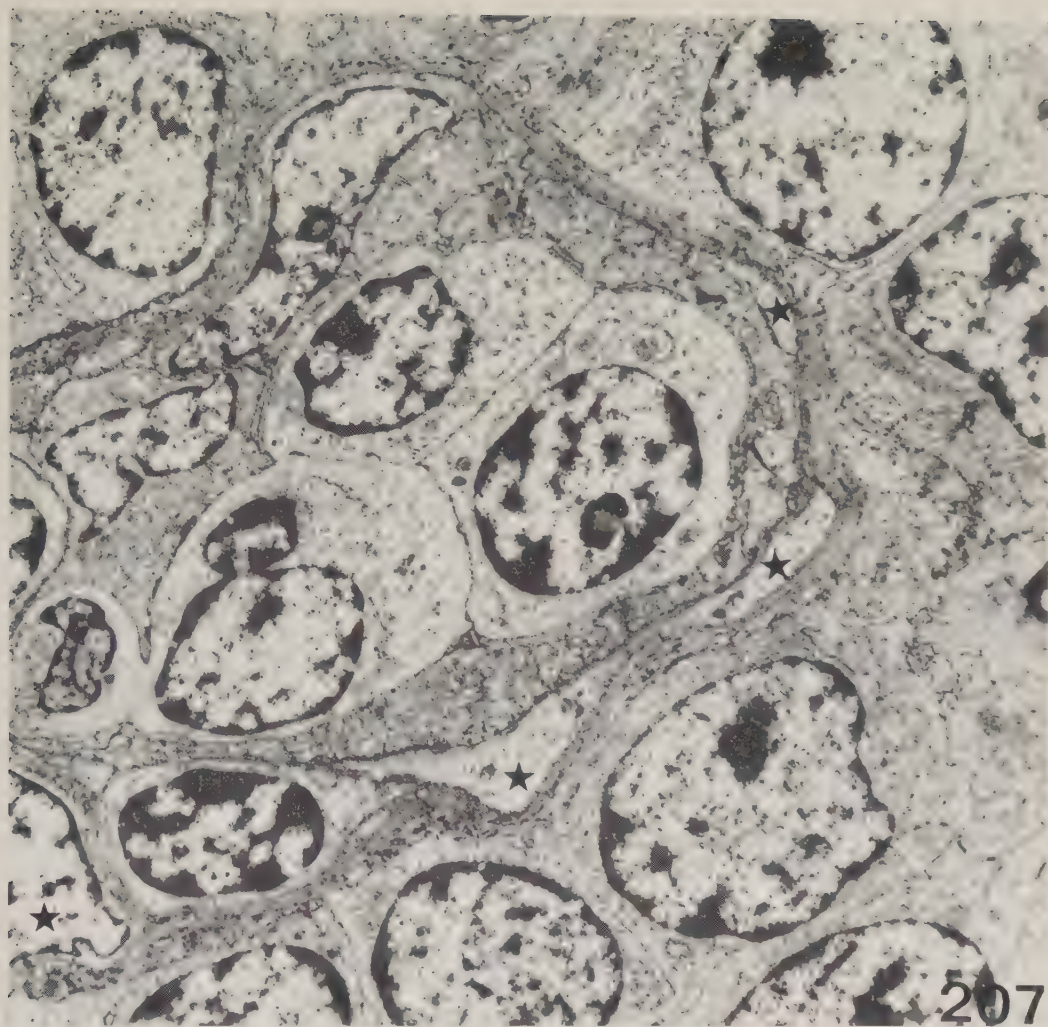
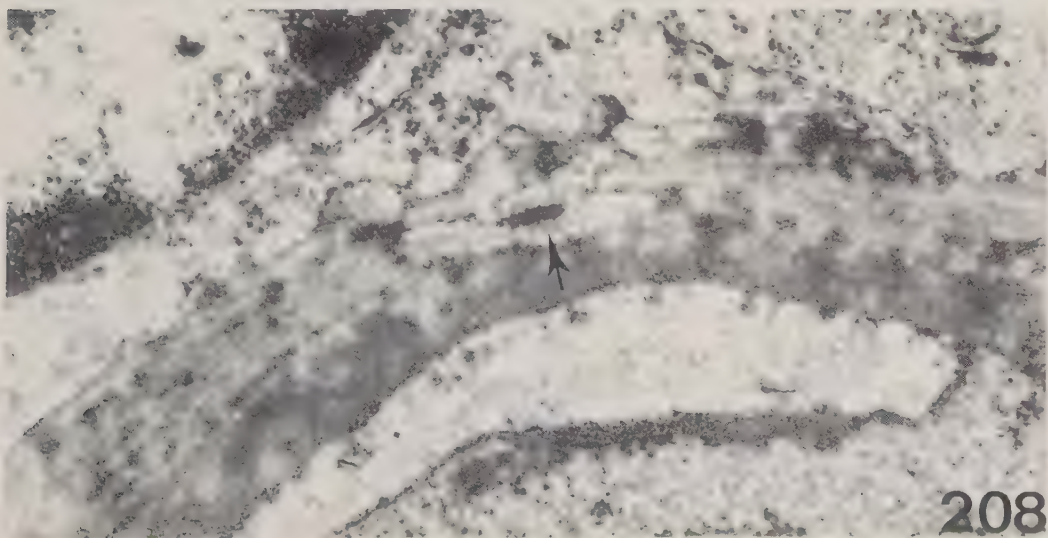


Fig. 207. High endothelium venule with lymphocyte stagnation. Tendency to development of interlocking processes between the lymphocytes within the lumen. Part of the nucleus of a pericyte in lower left part of the picture (asterisk). To the right of this is a lymphocyte within laminar duplications. Further to the right the cytoplasm of the pericyte is visible again (asterisks). At the uppermost asterisk there is a desmosomal connection between two cells within the basal membrane. A higher magnification of this field is seen in fig. 208. x 7700.

Fig. 208. Higher magnification of the field at the upper asterisk in fig. 207. Within a gap in the basal membrane is a desmosome (arrow). In serial sections this appeared to be an attachment point between the pericyte and the IF-cell on the outside of the membrane. x 55,000.



207



208

Fig. 209. A lymphocyte is seen passing through the thin, innermost lamella of the basal membrane of a venule (the lumen is compressed). On the outside of the membrane the cytoplasm appears "clear" and resembles the cytoplasm of the pericytes. x 7500.

Fig. 210. An immature cell is seen passing the basal membrane of a venule. It has a bud of cytoplasm on the inside of the membrane, connected to the cell body through a gap. The cytoplasm contains many polyribosomes and the nucleus has several nucleoli. The cell is considerably smaller than a fully developed IF-1 cell (this is approximately the largest diameter of the cell). It might represent a lymphocyte in transformation, developing into an IF-1 cell. x 7000.

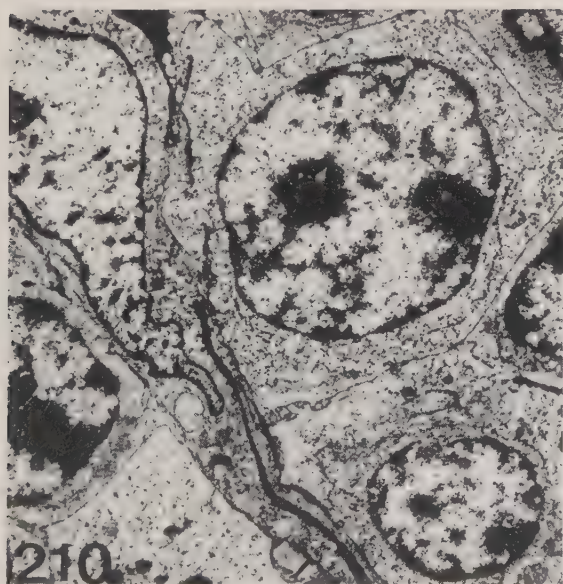
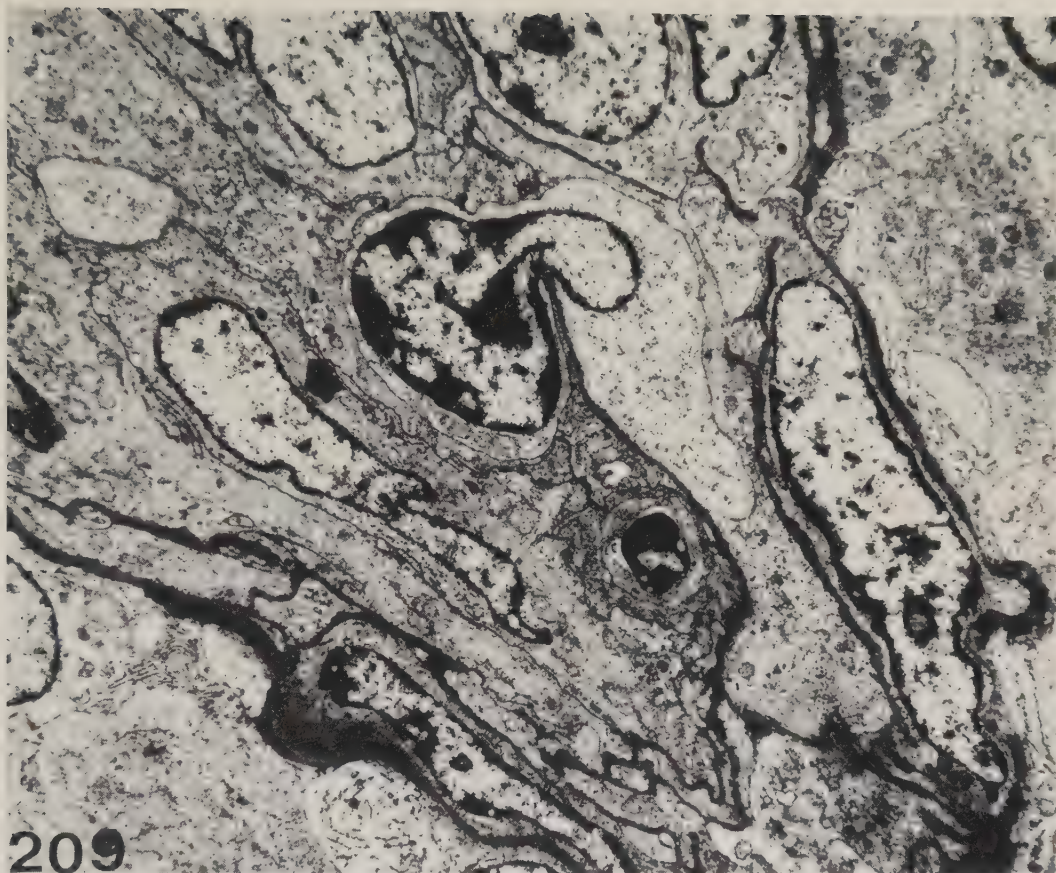


Fig. 211. The smallest type of vessel seen within the IF. It consists of a single row of low endothelial cells and a membrane split into at least two laminae. A lymphocyte within the lumen. On the outside of the basal membrane a cell with an irregular nucleus (arrow). Light microphotograph. Toluidine blue, x 1120.

Fig. 212. Electron microphotograph of the same vessel. The laminar duplications enclose a layer of clear cytoplasm, belonging to pericytes. The cell on the outside of the vessel has the character of a reticulum cell and contains bundles of filaments (arrow). Its cytoplasm is seen for long stretches along reticulum fibres radiating from the vessel wall. On the opposite side of the vessel is a lymphocyte apparently directly adjacent to the basal membrane. x 8100.

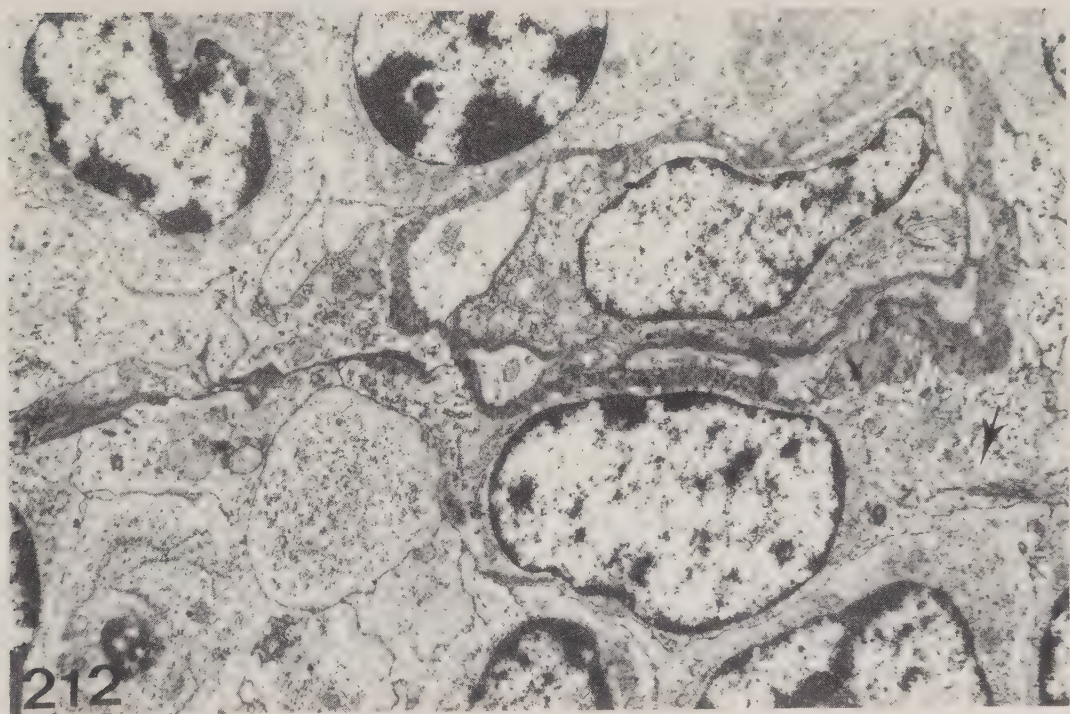
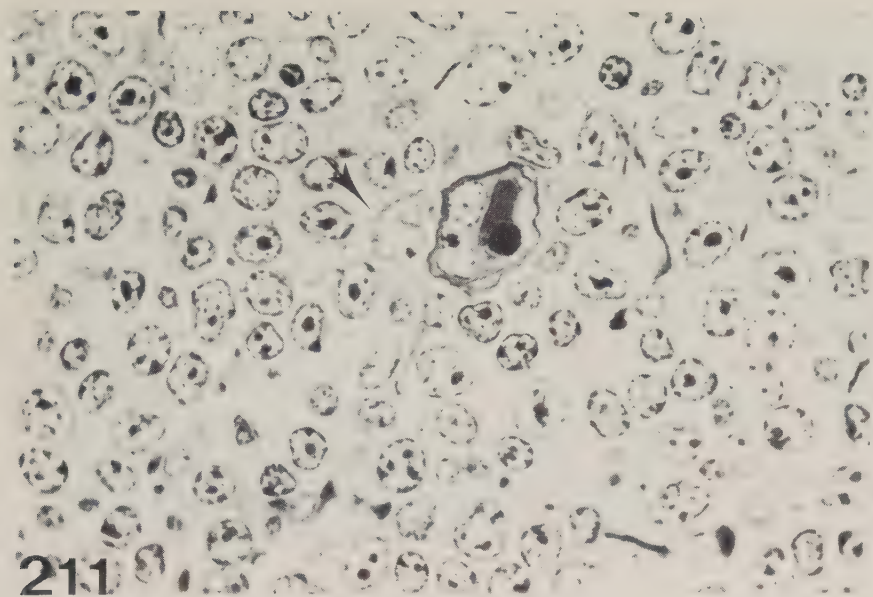
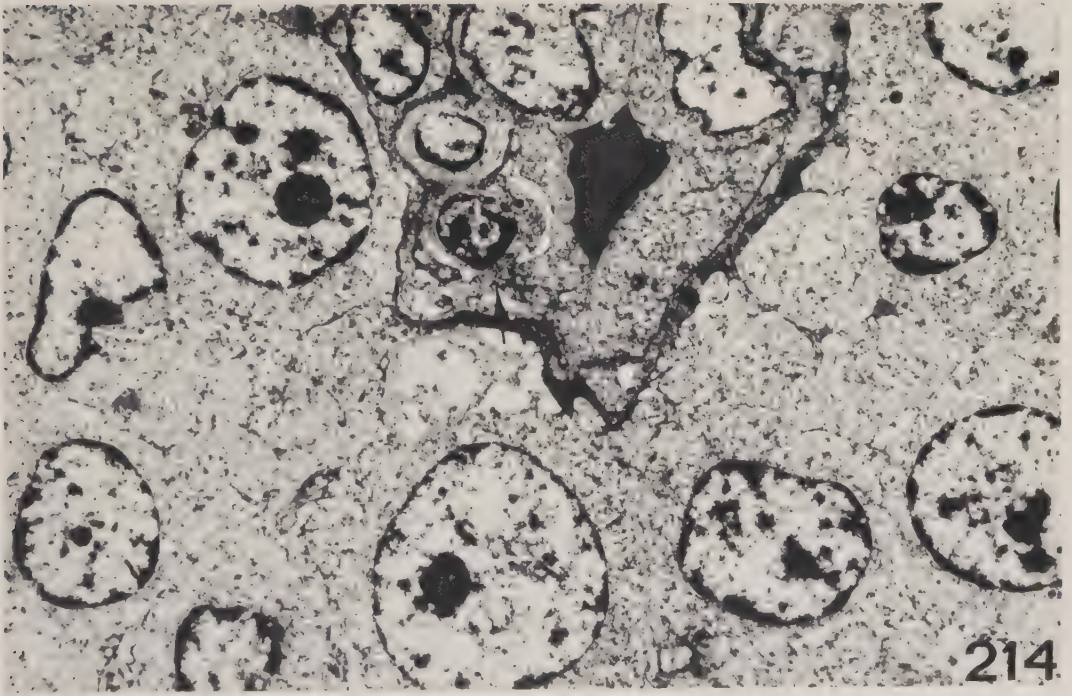
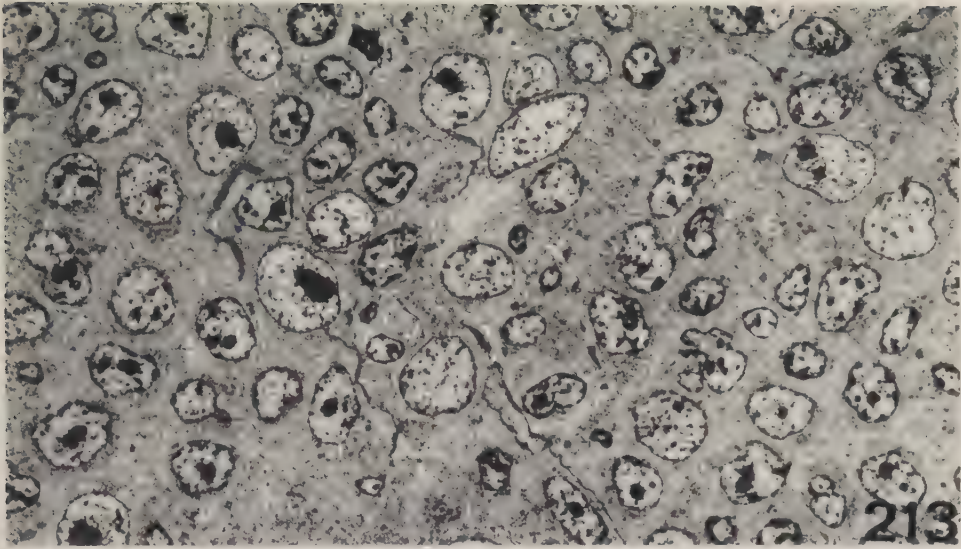


Fig. 213. Low power electron micrograph of lymph node biopsy of case 671/66 (LLD-2). The tissue is essentially similar to the IF of LLD-1. x 2000.

Fig. 214. Electron micrograph of lymph node biopsy of case 663/58 (LLD-2). The cells of the parenchyma are prolymphocytes identical to those of the IF of LLD-1. A venule is seen with a lymphocyte in transfer through the wall (arrow). x 8000.



DIAGNOSIS OF CASES REFERRED TO IN TEXT

		Fig.no.
198/57	LLD-4	
737/57	LLD-4	
98/58	LLD-1	112-113
136/58	LLD-1 + HL + myeloma	135
663/58	LLD-2	10-16, 214
397/59	LLD-4	64-65
690/60	LLD-3	
1120/60	LLD-3 + HL	33-38
225/61	Macroglobulinemia	89-90
413/61	Bone marrow group 3	105
451/61	LLD-4 + HL	40-43
929/61	LLD-2	
961/61	LLD-1 + HL	136-142
1059/61	LLD-4	
99/62	Macroglobulinemia	101-104
535/62	LLD-4	49
1095/62	LLD-1+2	106
185/63	LLD-1	5-6
655/63	Bone marrow group 2 + HL	163-170
1047/63	LLD-4	51-52
1124/63	LLD-1	
83/64	LLD-1 + HL	126
619/64	LLD-4	44
878/64	Undifferentiated lymphoma	110-111
1305/64	LLD-2	
1320/64	Bone marrow group 2	
1434/64	LLD-1 + HL	134
42/65	LLD-1 + HL	129-133
151/65	Bone marrow group 2	18-19
300/65	LLN + HL	53-54, 59
600/65	LLD-1	
762/65	LLD-4	
1147/65	LLD-3	26-28
1226/65	Bone marrow group 2	
1298/65	LLD-1 + HL	121-125
613/66	LLN	
671/66	LLD-2	17, 213
692/66	LLD-1 + Hodgkin's disease	118-119
963/66	LLD-4	45-48
31/67	LLD-1 + Hodgkin's disease	8-9, 115-117
109/67	Bone marrow group 1-3	82

437/67	Bone marrow group 1-3 + HL	72-80
614/67	LLD-1	
855/67	LLD-3 + HL	171-175
865/67	LLD-4	50
1404/67	LLD-1	
258/68	LLD-1	161-162
633/68	Undifferentiated lymphoma	109
663/68	Bone marrow group 2	
777/68	Macroglobulinemia + HL	96-100
1332/68	LLD-1	
204/69	Macroglobulinemia	
609/69	LLN + HL	179-180
737/69	LLN + HL	
829/69	LLD-1 + HL	1-2, 146-160
891/69	Macroglobulinemia	
1107/69	LLD-3	
290/70	LLD-3 + HL	176-178
705/70	LLD-3 + HL	20-25
820/70	Macroglobulinemia	83-85
831/70	LLD-1 + HL	127-128
1042/70	LLD-4	
1224/70	Macroglobulinemia + HL	86-88, 91-93
341/71	LLN + HL	57-58
V.434/71	Macroglobulinemia	94-95
586/71	LLD-1	
706/71	LLD-4	
902/71	LLD-1	
1029/71	Bone marrow group 1-3	
1140/71	LLD-3 + Hodgkin's disease	29-32
220/72	LLD-3	39
913/72	Bone marrow group 1-3	81
38/73	LLD-1 + HL	
219/73	LLN	55-56, 60-63
243/73	LLD-4	
V.251/73	Macroglobulinemia	
272/73	LLN + HL	
352/73	LLD-1	
486/73	LLD-4	
669/73	LLD-1 + HL	143-145
799/73	LLN + HL	66-71
841/73	Undifferentiated lymphoma	
1107/73	LLD-1	
2-219	LLD-1	3-4, 181, 183-212

